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BULLETIN OF
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OF MEDICINE



JANUARY 1944

ADDRESS OF WELCOME*

ARTHUR FREEBORN CHACE

President, The New York Academy of Medicine

TONIGHT we are gathered together for the opening of the Sixteenth Annual Graduate Fortnight of The New York Academy of Medicine.

It was at the suggestion of Ludwig Kast that the Fortnight was founded and the pattern which he then outlined has been followed from the beginning. It was his idea that we should devote the entire Fortnight to the study of a single subject which would be developed by lectures, daily hospital demonstrations, exhibits, moving pictures and presentations of fresh specimens. It is a source of satisfaction to me that Dr. Kast was given credit during his lifetime for having been instrumental in establishing this annual event and that his name will always be given to the first lecture of the series.

The Fortnight has a primary educational purpose with an especial appeal to the Fellowship and to the general practitioner.

The subject of *Disorders of the Digestive Tract* was chosen for this year because of the many basic advances which have been made in this specialty since it was taken up in the Fortnight about ten years ago. It is also a most timely subject since experience has shown that in war time there is a distinct increase in disturbances of the gastrointestinal tract among both the military and the civil population. Worry.

* Delivered October 11, 1943 at the 16th Graduate Fortnight of The New York Academy of Medicine.

bad dietary habits and overwork aggravate peptic ulcer. In England it was found that perforated peptic ulcer increased by a third, and six times the usual number in areas subjected to severe air raids.

The Academy wishes to express its appreciation to Mr. R. Thornton Wilson for his great generosity in establishing the Florence Ellsworth Wilson Memorial Fund in support of the Graduate Fortnight. The income from this fund will make it possible to perpetuate the Fortnight and to maintain the high scientific standards which it has followed since its inception. It is of inestimable value in defraying the expense of bringing eminent scientists from distant places to speak to us. We are especially honored to have Mr. Wilson on the platform with us tonight so that we may endeavor to express our deep gratitude to him for his munificent gift. No more fitting tribute to the memory of a distinguished and charitable woman could have been conceived than this living memorial which will endure through the years.

In this program you see the result of almost a year's work on the part of your Fortnight Committee, for immediately upon the ending of one Fortnight, the Committee must begin preparations for another.

I hope you will find time to attend the hospital clinics, the exhibits, the evening lectures and the panel discussions.

The Committee has not only given you the opportunity to see the results of recent research in this specialty, but has also placed before you most important techniques which you will find useful in practice.

We have been greatly encouraged in studying our records of the attendance at the Graduate Fortnight, to find that year after year, not only many of the same men have returned, but also that until interrupted by the war, the attendance had steadily increased.

We feel most strongly that it is our duty to carry on all our civilian activities during the war period so that when our Fellows return from military service they will find awaiting them, in printed form, the lectures that will bring them up to date on the forward march of medicine, for the Academy must do its share in scientific advancement during the war as well as when peace returns.

In the name of The New York Academy of Medicine, I welcome you to this intellectual feast which has been prepared for you by the leading scientists and medical men in this most important specialty. We trust that you will carry away with you not only the thirst for greater knowledge but that you will continue your routine of work with renewed enthusiasm and inspiration.

SOME RECENT DEVELOPMENTS IN THE PHYSIOLOGY OF THE STOMACH AND INTESTINE WHICH PERTAIN TO THE MANAGEMENT OF PEPTIC ULCER*

A. C. IVY

Nathan Smith Davis Professor of Physiology, Northwestern University.

I CONSIDER it a distinct honor to have been invited to deliver this lecture in memory of Doctor Ludwig Kast, who manifested his devotion to the Profession of Medicine in many ways, only two of which I shall mention. One was to propose this Graduate Fortnight, which is well known and highly regarded throughout our Country. The other was the service he rendered to the advancement of Medical Science by his perspicacious administration as President of the Josiah Macy, Jr. Foundation.

It is appropriate on this occasion to present, first, a development in which Dr. Kast manifested much interest and which he facilitated in his capacity as President of the Foundation. *This development pertains to the possibility that a patient may be "immunized" against the recurrence of peptic ulcer by the intramuscular injection of an extract of duodenal mucosa containing enterogastrone.*

ENTEROGASTRONE

It has been well established that fat and sugar acting in the intestine in an adequate concentration inhibit gastric secretion and motility by the production of a chalone called enterogastrone.^{1,2,3} Extracts of the upper intestinal mucosa have been prepared, which when injected parenterally, inhibit gastric motility and gastric secretion, regardless of the type of stimulus.

It has been postulated that since fat in the intestine and relatively crude extracts (pyrogen free) of intestinal mucosa inhibit both gastric secretion and motility, that only one active principle, namely, enterogastrone is concerned. The results of recent experiments in our labora-

* The Ludwig Kast Lecture, given October 31, 1943 at the Sixteenth Graduate Fortnight of The New York Academy of Medicine.

tory show that preparations (pyrogen free) can be made which inhibit gastric secretion without inhibiting motility in the doses used.⁴ In fact, the preparation which we have been and are using in patients with peptic ulcer and in preventing ulcers in animals does not inhibit motility in the dose employed. Thus, it is becoming more evident that the principle which is responsible for inhibiting gastric secretion is different from that which inhibits gastric motility.

It was discovered in different laboratories that the urine of man and dog contains substances which inhibit gastric secretion and motility. This suggested the hypothesis that the urinary substances represent excreted enterogastrone.^{5,6,7}

UROGASTRONE

Because it was uncertain whether the urinary gastric inhibitors were identical with duodenal gastric inhibitors, the former were termed *urogastrone* to distinguish them from enterogastrone.

It is clear that the feeding of a high or low fat diet increases the amount of urogastrone in human and canine urine.⁸ In addition there is evidence which indicates that the patient with peptic ulcer excretes less urogastrone than non-peptic-ulcer subjects. In 8 patients with peptic ulcer on a milk and cream diet less urogastrone was excreted even than by fasting normal men.⁸ (In such experiments it is necessary to collect the urine fresh and to avoid bacterial action, otherwise much pyrogen is formed. In our experiments additional precautions are taken to remove pyrogen, and rectal temperatures are taken to make certain that pyrogen is not present.)

A serious attempt was made to ascertain whether urogastrone was produced by the intestine. A number of animals were enterectomized. In such animals the excretion of gastric inhibitory substances from the urine was regularly reduced but not abolished. When a "control operation" was performed, the excretion was increased. This latter observation rendered the interpretation of the results obscure. More than one gastric inhibitory substance may exist in the urine, some being specific and others non-specific in nature.

Steps to concentrate "one" of the gastric inhibitors in the urine have met with considerable success. Five-tenths of a milligram of the best preparation represents a gastric secretory inhibitory unit.⁹ This particular urogastrone has properties which differ from those of entero-

gastrone. One of the differences is that pepsin has no effect on this urogastrone while it inactivates enterogastrone. This shows that there is a urogastrone in human and canine urine which is not identical with enterogastrone. The source of this urogastrone is uncertain; it may even be a metabolic product of enterogastrone.

It has been clearly shown that the subcutaneous administration of urogastrone inhibits gastric secretion in man in doses which do not affect body temperature or cause immediate side reactions.¹⁰ This preparation was not used clinically in peptic ulcer patients because it caused a local swelling about the site of injection which appeared several hours later. However, we have been able to prepare a concentrate of enterogastrone which does not irritate the tissues locally and which we have injected intravenously and intramuscularly in numerous human and canine subjects.¹¹

THE "IMMUNIZATION" OF DOGS AGAINST GASTROJEJUNAL ULCER

To determine whether our enterogastrone would prevent the development of gastrojejunal ulcer, we used the Mann-Williamson (M-W) preparation. This preparation consists of a gastrojejunostomy in which the alkaline bile and pancreatic juice is diverted to the last 15 cm. of the ileum.

The prevention of ulcer: In Table I it will be noted (a) that when the animals are not treated 98 per cent die with ulcer in from 1 to 9 months; (b) that 10 dogs which were injected with an extract of muscle, treated as for the preparation of enterogastrone, all died of ulcer in 1 to 7.5 months; and (c) that of 33 dogs which received our enterogastrone preparation intravenously or subcutaneously only 25 per cent developed ulcer.

The fact that 25 per cent developed ulcer we cannot explain adequately. Either they became refractory to the material or the dose was not sufficiently large. It is interesting, however, that we have found in the course of our assays of enterogastrone that 25 per cent of dogs become refractory.¹¹

"Immunization" against ulcer: After preventing ulcer in the dogs for one year, the treatment was stopped with the idea that an ulcer would occur and then we could ascertain the "healing properties" of the treatment. *To our surprise*, ulcer did not occur in 11 dogs during

TABLE I

RESULTS OF THERAPY WITH ENTEROGASTRONE
INTRAVENOUSLY AND SUBCUTANEOUSLY

| <i>Group</i> | <i>No. of Dogs</i> | <i>Average Longevity Months</i> | <i>Range of Longevity Months</i> | <i>Per Cent Develop- ing Ulcer</i> |
|--|----------------------------|---|--|--|
| Dietary Control | 112 | 3.8 | 1—9 | 98.2 |
| Muscle Extract Control | 10 | 3.9 | 1—7.5 | 100 |
| Enterogastrone Treated Intravenously | 25 | | | |
| 6—developing ulcer while on treat- ment | | 6.7 | 4.2—9.2 | 25 |
| 8—dead of causes other than ulcer.... | | 4.7 | 1.5—9 | |

11—alive at 1 yr. without ulcer, proven by exploratory.

Treatment of the 11 dogs was stopped after 1 yr.

7 of 11 are now alive 17 to 24 months after cessation of treatment without ulcer.

3 of 11 died from causes other than ulcer in from 11 to 12.5 months after cessation of treatment.

1 of 11 died with ulcer 18.0 months after cessation of treatment.

| | | | | |
|--|---|-------|--|----|
| Enterogastrone Treated Subcutaneously | 8 | | | |
| 2—developed ulcer | | 4—4.5 | | 25 |

6—are alive without ulcer for 1 yr. and off of treatment for 2.5 months without ulcer.

one year without treatment. This surprised us because in previous work it was found that when ulcer was prevented with aluminum phosphate or gastric mucin, an ulcer developed in from 1 to 4 months, or an average of about 2 months after cessation of the treatment. But with enterogastrone 7 of the 11 animals are still alive without ulcer from 1.5 to 2 years after cessation of treatment, and only one of the 11 animals died of ulcer after the cessation of treatment.

TABLE II

THE EFFECT OF ENTEROGASTRONE AND OLIVE OIL ON
PEPSIN SECRETION

| Procedure | Volume cc. | | | Free Acid Total Output mgm. | | | Pepsin Concentration M.U./cc. | | | Pepsin Total Output M.U. | | |
|--|---------------|------|-----|-----------------------------------|-----|-----|-------------------------------------|------|-----|--------------------------------|-----|-----|
| | C | E | % | C | E | % | C | E | % | C | E | % |
| Denervated Pouch Pilocarpine and Enterogastrone .. | 23.0 | 11.1 | —52 | 59.2 | 9.3 | —84 | 964 | 1269 | +32 | 25M | 14M | —42 |
| Innervated Pouch Pilocarpine and Enterogastrone .. | 12.9 | 5.5 | —57 | 27.7 | 6.2 | —78 | 1160 | 1400 | +21 | 14M | 7M | —48 |
| Denervated Pouch Pilocarpine and Olive Oil | 42.1 | 28.0 | —33 | 129 | 64 | —50 | 940 | 936 | 0 | 32M | 25M | —22 |
| Innervated Pouch Pilocarpine and Olive Oil | 87 | 3.6 | —59 | 12.2 | 0.2 | —98 | 1450 | 550 | —62 | 12M | 2M | —84 |

MECHANISM OF THE "IMMUNIZATION"

Acid Production: Gastric analysis was performed on a group of untreated control as well as the treated animals. The treated animals manifested less tendency toward a prolonged secretory response to a meal. The differences however were not statistically significant. When an alcohol test meal was used it produced an abnormally prolonged secretory response in the treated animals as well as in the controls (M. I. Grossman). Thus, the evidence failed to show that the enterogastrone had effected an "immunization" by depressing gastric secretion.

Pepsin Production: The data in Table II (M. I. Grossman and H. Greengard) show that enterogastrone decreases total pepsin output, but does not abolish it. Ample pepsin remains to carry on normal gastric digestion. Further, it has been found (M. I. Grossman) that our "immunized" dogs secreted normal amounts of pepsin in response to an alcohol test meal.

Comment: Thus, we do not possess a proven explanation for the nature of the "immunization."

It is reasonable to hypothesize that the injections have increased the resistance of the jejunal mucosa to ulceration. It has been clearly established that the corrosive action of unbuffered gastric juice is the chief cause of jejunal ulcer in M-W dogs. The nutritional disturbance incident to the operative interference with normal digestion is another factor. And, a third factor is that the jejunum is more sensitive to the irritating action of gastric juice than the duodenum.

It should be recalled that Sandweiss, Saltzstein and Farbman¹² have observed that ulcer can be prevented in M-W dogs by the injection of a urine extract. The results of their studies indicated that the substance acted not by depressing gastric secretion but by promoting repair of the mucosa. More recently Sandweiss¹³ has reported that the administration of his urinary product to M-W dogs also confers an "immunity" against recurrences.

THE USE OF AN ENTEROGASTRONE PREPARATION IN MAN

To date we have administered our enterogastrone preparation to some 15 patients, who have given a history of 2 or more recurrences of peptic ulcer annually. Palliative results have been obtained. However, sufficient time has not elapsed to determine whether any "immunization" has occurred. Considerable time and statistical data will be required to ascertain whether the human patient will react similarly to the dog.

Our animal experiments, at least, have provided a basis for the hope that in time we may be able to "immunize" patients against repeated recurrences of peptic ulcer.

THE RESPONSE OF THE HUMAN STOMACH TO CAFFEINE AND COFFEE

Many physicians in the management of patients with peptic ulcer interdict the use of alcoholic beverages and smoking. Very few interdict the use of coffee.

Alcohol: It is well established that alcohol in concentrations of less than 20 per cent stimulates gastric secretion. In fact, alcohol stimulates gastric secretion when administered by any route. There is good evidence to show that alcohol stimulates, even when given intravenously, by causing the release of histamine from tissues.^{14, 15} Since it is certain that high acidity and irritants contribute to the chronicity of peptic ulcer, it is rational to interdict alcohol.

Smoking: It is uncertain why so many ulcer patients improve after giving up smoking. Smoking increases the acidity of the gastric contents in some subjects when the alcohol test meal is used,¹⁶ though we have never seen it stimulate gastric secretion materially in the fasting stomach.¹⁷ Smoking inhibits gastric motility, and by inducing retention smoking may increase the acidity of the gastric contents. As a result of our studies¹⁷ on the effect of smoking on the gastrointestinal tract, in which we observed depression of gastric activities in all but 2 of 60 subjects, we suggested that the deleterious effects of smoking on the stomach may be secondary to cardiovascular changes. We observed the greater changes when the subject reached or strained his tolerance. It is of interest in this connection that Wolf and Wolff,¹⁸ observed marked pallor of the gastric mucosa and depression of motility and acid secretion when their "Alexis St. Martin" strained his tolerance for tobacco.

Caffeine: There are some 30 articles in the literature dealing with the effect of coffee and caffeine on the stomach. Most of the articles because of defective technique or because they used the dog as an experimental animal conclude that coffee and caffeine are without effect on gastric secretion. Some authors, however, have suggested the use of coffee as a test meal, and tea and toast has been used extensively as a test meal.

My attention was first attracted to caffeine when a physician reported to me a patient who apparently developed ulcer on consuming daily some 20 bottles of a beverage containing caffeine. I informed him that I had on several occasions administered caffeine to dogs without observing a stimulation of gastric secretion. Dr. J. A. Roth and I decided to study the subject when Dr. Owen Wangensteen told me that E. S. Judd¹⁹ had produced duodenal and gastric ulcers in cats and guinea pigs by administering caffeine in bees' wax subcutaneously.

The production of ulcer in cats with caffeine. We have confirmed the observations of Judd.¹⁹ Acute and chronic ulcers of the stomach and duodenum can be produced in cats by the administration of 5 grains of caffeine daily. In fact, in some cats the intravenous administration of a single dose of 2 grains of caffeine will cause within a few hours hemorrhagic erosions, acute ulcers and areas of marked vasoconstrictor spasm in the gastric mucosa.

The latter dose on a body weight basis would amount to 30 to 60

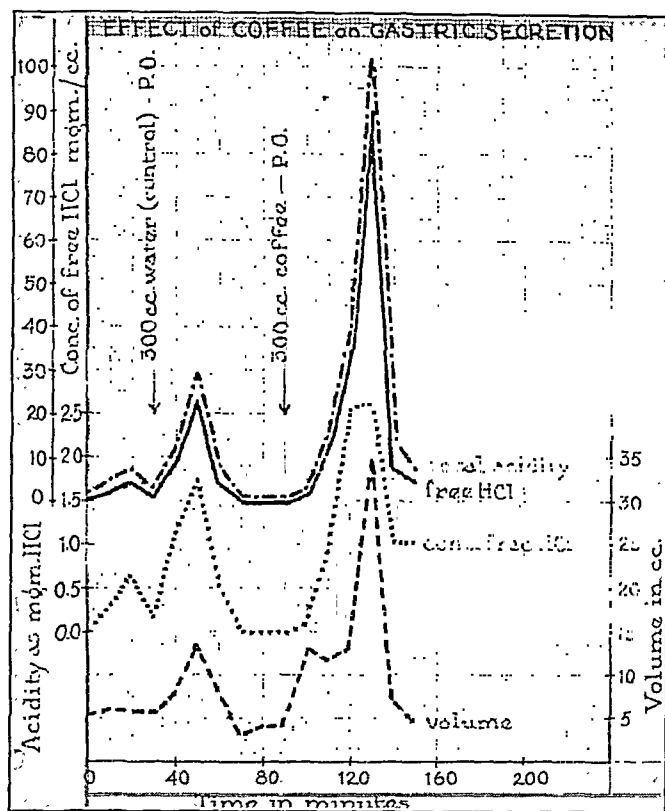


Fig. 1

grains of caffeine daily in man. Thus, if the human stomach responds like the cat's stomach, *the abuse* of coffee or beverages containing caffeine may be a direct cause of ulcer in susceptible patients.

The Stimulation of Gastric Secretion by Caffeine, Coffee and Sanka:

Dog. As others have found, ordinary doses of caffeine do not stimulate gastric secretion in the Heidenhain or Pavlov pouch dogs.

Cat. One grain of caffeine administered intravenously or intramuscularly to cats stimulates a flow of gastric juice of high acidity. This effect is decisively inhibited by atropine.

Man. Dr. Roth's observations on man may be summarized as follows:

The intramuscular injection of 4 grains of caffeine base, as caffeine sodium benzoate, causes a copious secretion of gastric juice. The response is usually completed in 1 hour though some subjects secrete at a high level for 2 or 3 hours. The oral administration of the same dose in 200 c.c. of water stimulates to about the same extent, and 1 mg. of atropine sulphate subcutaneously decidedly reduces but does not abolish

the response. A dose as small as 1.2 grains of caffeine orally in 200 cc. of water definitely stimulates.

300 cc. of coffee (Figure 1) given via the stomach tube, to avoid psychic stimulation, decidedly stimulates gastric secretion. In some subjects the response is completed in 1 hour, in others the response continues for 2 or 3 hours. 300 c.c. of "Sanka," which contains somewhat more than 1.0 grain of caffeine also stimulates gastric secretion.

50 cc. of 7 per cent alcohol and 4 grains of caffeine manifest a synergistic stimulation of gastric secretion. Thus, *the practice of drinking coffee in relation to alcoholic beverages places the stomach and duodenum of the person susceptible to peptic ulcer under considerable strain.*

We were particularly interested in ascertaining whether caffeine and histamine acted synergistically on the gastric glands. This is because it is strongly presumptive that that portion of the gastric secretory response in the ulcer patient which is not abolished by atropine is due to histamine. *Our results on normal subjects show that histamine and caffeine act synergistically in stimulating the gastric glands.* For this reason, I suspect that when we study the response of patients with peptic ulcer to caffeine and coffee, a very low threshold to caffeine stimulation will be found.

SUMMARY

1. The results of experiments on animals provide a basis for the hope that in time we may be able to increase the resistance of the gastric and duodenal mucosa to ulceration and decrease the incidence of recurrences of peptic ulcer in susceptible patients.

2. There is substantial laboratory evidence supporting the view that the consumption of alcoholic beverages, excessive smoking and the excessive use of coffee so affect the gastric mucosa and glands as to predispose to gastroduodenal ulceration in susceptible subjects.

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BENIGN AND MALIGNANT LESIONS OF THE STOMACH *

ARTHUR W. ALLEN

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THE differential diagnosis between benign and malignant lesions of the stomach is often impossible by any of the clinical diagnostic methods known. The physician, the roentgenologist, the gastroscopist, and the surgeon may be in doubt or completely wrong concerning the true nature of the disease until the pathologist has examined the specimen microscopically. Since there is ample opportunity to treat a malignant lesion under the impression that it is benign, we must weigh the evidence carefully in each case. All doubtful ulcerations and tumors should be widely resected, since by this method alone can we give the patient, in the early stages of cancer, his greatest chance for cure. The added procedure, under these circumstances, rarely jeopardizes the outcome, if the microscopic studies finally prove the non-malignant nature of the pathological process. On the other hand, the radical attack will materially increase the number of cures in this group of patients.

BENIGN LESIONS

Benign lesions of the stomach include simple ulcer, anastomotic ulcer, gastrojejunocolic fistula, leiomyoma, gastritis, polyposis, and syphilis. Those considered malignant at any stage are carcinoma, sarcoma, and lymphoma. That some of the disorders in the benign group may become malignant has been established. Often, it has been said that benign ulcer may undergo malignant degeneration. This is probably true in a small percentage of such lesions, since one does occasionally find cancer cells on the edge or one side of benign ulcer. The leiomyomatous tumors may be entirely benign but often are found to be sarcomatous. Whether these processes are always benign at some early stage of their development is difficult to establish. It is probably true that adenomatous polyps begin as a benign process but in ulcer

* Read October 12, 1943 at the Sixteenth Graduate Fortnight of The New York Academy of Medicine.

and the leiomyomatous lesions, they are probably either benign or malignant from their beginning. The speed with which tumors of the stomach develop, varies tremendously. A fulminating inoperable cancer may be encountered in a person enjoying perfect health until a few days before seeking medical advice. On the other hand, one finds a good story with all evidence that years have passed before a malignant lesion has produced sufficient invalidism to excite the suspicion of the victim or the clinician. The fact that cancer of the stomach accounts for more deaths than any other malignant lesion in this country, should certainly be sufficient reason to warrant the possibility of this diagnosis with greater frequency in the borderline and early stage cases.

Polyps of the stomach may cause little in the way of symptoms other than anemia. Severe blood loss does occur and usually this is gradual and insidious. A condition resulting from polyposis, difficult to differentiate from pernicious anemia, is occasionally seen. Acute sudden hemorrhage of massive degree occurs rarely.¹ If the polyp occurs in the antrum and is attached by a long stalk, symptoms of intermittent pyloric obstruction are the rule. Achlorhydria is present in nearly all cases. In a study of the cases of polyposis of the stomach occurring in the Massachusetts General Hospital, we found that malignant degeneration had occurred in 41 per cent of the cases.² Pearl and Brunn have recently reported a new collected series in which 50 per cent had become malignant.³ They state that two types of polyps occur—those of congenital or neoplastic origin, and those that are secondary to an inflammatory process. It is obvious, if the polyps are few and pedunculated, that they may be removed by gastrotomy. If they are numerous or sessile in type, that portion of the stomach involved must be resected.

Leiomyoma is a rare tumor of the stomach, occurring in 1 per cent of our cases of hemorrhage from the upper gastrointestinal tract. They are sometimes recognized in routine gastrointestinal examinations before symptoms of this lesion occur. More often, however, the diagnosis is made following a severe massive hemorrhage. Usually such patients are suspected of having cancer of the stomach from the lack of digestive disturbances, the onset of sudden bleeding, and the tumefaction seen in the roentgenograms. Actually, the appearance in the films and the gastroscope are characteristic. The smooth rounded tumor with an umbilicated center cannot easily be mistaken for any other

lesion. The hemorrhagic tendency is easily explained when one investigates the central depression, since this will be found to lead to a blood vessel in the stomach wall. The most usual location is the lesser curvature and the bleeding vessel, a branch of the left gastric artery. Many of these are of neurogenic origin as pointed out by Ransom and Kay in a review of the pathology of such lesions appearing in their clinic.⁴ Many of them are benign and if one could be sure of this, a simple excision of the tumor would suffice. On the other hand, we find that the appearance of the tumor is not always a reliable guide and some that appear benign turn out to be sarcomatous. It is probably safe to locally excise the small symptomless tumors, particularly, if they occur near the cardia and are inaccessible. The rule for those appearing in the more accessible regions and those of sufficient size to have caused severe bleeding, as well as those with obvious extension through the serosa, should be wide resection.

Gastritis is now recognized with greater frequency since the roentgenologist has learned its characteristic picture and the gastroscopist has become an important member of our diagnostic group.⁵ That severe and even fatal hemorrhage can result from gastritis, we have long been aware. It is necessary to place this malady in its proper sphere and not assume that it is to be expected only as an accompanying lesion to ulcer of the stomach and duodenum. It is usually precipitated by the ingestion of irritating foods, condiments, and alcohol. Occasionally, one meets this situation in an individual of exemplary habits of diet, etc., only to find that stress and strain of an emotional type may be the only activating factor. High acid levels in the gastric contents are the rule. In the usual case not associated with other complications, one finds a gratifying response to proper palliative treatment, consisting of a bland smooth diet, bed rest, and the elimination of psychic disturbances. Often, it is necessary to begin treatment by complete physiological rest of the gastrointestinal tract, until the acute phase has subsided. Blood transfusions, intravenous fluids, salt, glucose, vitamins, and amino acids are often helpful.

Severe gastritis, producing repeated severe hemorrhages and almost complete invalidism, has occurred in two patients in our clinic following the Billroth II type operation for duodenal ulcer. These patients had had the pylorus and first portion of the duodenum removed, the antrum closed, and a posterior gastrojejunostomy done. Finally, radical

operation was undertaken and both have been completely relieved by a subtotal gastrectomy, which included the old anastomosis. In neither of these patients was there any evidence of duodenal or anastomotic ulcer at the time of the last operation. Both had an extremely virulent type of hypertrophic gastritis. In no case in my experience has it been necessary to subject a patient with uncomplicated gastritis to surgery, although in a few instances of stubborn resistance to palliative management, it has been considered.

Syphilis of the stomach, producing disabling symptoms, is met rarely in our clinic. Usually the diagnosis has been mistaken for carcinoma and the operation undertaken because of the lack of response to anti-luetic treatment. It must be remembered that a positive serological test is no indication that a lesion of the stomach resembling cancer is syphilis. Williams and Kimmelstiel⁶ have brought out some of the more logical points of differential diagnosis. Patients have withstood radical operation for this lesion well and should be offered the benefit of surgery in all doubtful cases.

Anastomotic ulcer and *gastrojejunocolic fistula* are complications of inadequate surgery for duodenal ulcer. Although these lesions demand radical procedures involving the stomach, they are not primarily of stomach origin and will not be further considered in this discussion.

Gastric ulcer is by far the most common benign lesion in the stomach. It is much less frequent than duodenal ulcer, and our conception of its management has been materially influenced by a greater experience with the duodenal lesion. The term "peptic ulcer," so long in use, has confused the issue to some extent. Since duodenal ulcer responds so well to palliative methods, in the majority of cases, it has led us to a dangerous and careless attitude regarding gastric ulcer. In a series of 255 cases diagnosed and treated as benign gastric ulcer in our clinic, we found that 14 per cent of them finally proved to have cancer.⁷ It was obvious to us that the differential diagnosis was often impossible until the microscopic sections were studied. We analyzed the records of this group of patients carefully to determine findings that might lead to a more accurate diagnosis.

Healing of the ulcer area, under ideal hospital treatment, was of disappointing value in this group. Patients with proven cancer often lost their symptoms, regained lost weight, and by roentgenographic and

gastroscopic studies appeared to have healed their ulcerations. This, we believe, may be explained by the subsidence of the surrounding inflammatory reaction and by the temporary filling in of the crater by cancer cells or granulation tissue. Since we know that this false impression can occur, it becomes all the more necessary to keep a careful watch of these patients and see that they return for observation within a month of discharge from the hospital.

The persistence, type, and radiation of *pain* in gastric ulcerations was also of little help in the diagnosis. Some patients with symptoms, controlled only on hospital management, finally proved to have cancer. On the other hand, lesions that failed to respond to the best palliative regimen that could be outlined for them, finally showed no evidence of malignancy by microscopic studies.

The *location* of the ulcer was of considerable help. Sixty-five per cent of the ulcers in the immediate prepyloric region and 90 per cent of those on the greater curvature proved to be malignant, while 20 per cent of those involving either the anterior or posterior walls and 10 per cent of those of the lesser curvature, proved to be cancer. These data are somewhat misleading since half of all the ulcerations of the stomach coming to our clinic were located on the lesser curvature. In this most common site, we found the majority of our errors in diagnosis.

The *size* of the ulcer gave some indication of its true nature. The average diameter of those proved benign was 1.7 cm., while the malignant group averaged 2.3 cm. Two ulcers in the prepyloric region, less than 1 cm. in diameter, were malignant. One enormous lesion, requiring total gastrectomy under the diagnosis of unfavorable cancer, proved to be benign ulcer. Therefore, it is impossible to rely on the size of the ulcer as an infallible guide. In the majority of cases, however, the small ulcer will prove to be benign while the large lesion will be malignant.

Free *acidity* of the stomach contents in proven cancer in our hospital was absent in 60 per cent of the cases. In the "ulcer-cancer" group, free acid was found in those proving to be cancer in the same high proportion as was observed in benign ulcer. Therefore, we may expect malignancy in the achlorhydriac stomach but cannot depend on the finding of acid in the stomach contents to rule out cancer.

The *age* of the patient and the *duration* of symptoms were evalu-

ated in respect to differential diagnosis with considerable helpful evidence. In patients beyond the age of fifty with symptoms of less than one year, the lesion proved to be cancer five times as often as benign ulcer. If, on the other hand, symptoms had been present for over five years, the reverse was true in this same age-group. In the younger patients, the duration of symptoms did not help in the differential diagnosis. It has long been known that indigestion associated with gastric ulceration, beginning after the age of forty, is very likely to prove to be due to cancer.⁸

Medical management of benign gastric ulcer is not as effective as it is in duodenal ulcer. In a recent study by Judd and Priestley,⁹ they found that less than 50 per cent of patients with gastric ulcer were satisfactorily maintained on a medical regimen. In their group, 10 per cent of gastric ulcerations finally proved to be due to cancer. Surgical treatment gave satisfactory results in all but 1 of 162 patients who survived operation.

We have been impressed by the safety of gastrectomy for gastric ulcer as compared to the same type of operation for duodenal ulcer. In 65 consecutive operations for gastric ulcer in our clinic, there was only 1 death. This is due to the lack of difficulty in management of the duodenal stump when it is normal and free. When duodenal ulcer with its inflammatory extension is dealt with, there is in many instances the problem of a satisfactory turn-in of normal duodenum.

In our group, the five-year cure-rate was raised to 40 per cent when the operation was undertaken on the diagnosis of ulcer and cancer was found microscopically. This is double the percentage of five-year cures observed in our clinic when the operation was carried out on the clinical diagnosis of cancer.¹⁰

When one considers the difficulty in differential diagnosis, the relatively unsatisfactory results of medical treatment, the increased safety of radical surgery, and the marked improvement in end-results in these with early cancer, we have a strong argument in favor of considering gastric ulcer as primarily a surgical lesion.

MALIGNANT LESIONS OF THE STOMACH

Lymphoma produces a tender, often palpable, lesion of the stomach. This lesion rarely comes to the surgeon at an operable stage; usually there is associated extensive lymph node involvement. The diagnosis

is usually confirmed by biopsy. Fortunately, these lesions are radio-sensitive to a surprising degree. Long respites and possible cures have been reported. Recurrences of the disease and widespread metastases respond less well to therapy. When possible, a combination of surgery and radiation gives the best results.¹¹

Sarcoma of the stomach occurs with slightly greater frequency than lymphoma and both lesions are comparatively rare. In reticulum cell sarcoma, there is evidence that postoperative radiation is of value.¹² In some of the other forms of sarcoma, radiation seems to have less to offer. In all cases, wide resection with involved nodes should be done when possible and all should have the benefit of postoperative roentgen radiation.

Cancer of the Stomach occurs with such frequency that one should exert every effort towards the education of the laity regarding this possibility. The people should know that approximately 35,000 deaths occur each year in this country from this cause.¹³ So far, the only effective attack on the disease is by surgical extirpation. The earlier the lesion at the time of operation, the better the prognosis. Advertising of indigestion cures should be prohibited by legislation.

The physician has the responsibility of thorough investigation of patients with symptoms and signs of early cancer of the stomach. Indigestion beginning after the age of forty, anemia, anorexia, fatigability, and weight-loss should lead to a careful consideration of the stomach. Too often, investigation has been postponed until the patient is beyond the help of surgery. By a careful evaluation of the situation, many early and curable lesions can be recognized.

The surgeon has gradually increased the operability rate of carcinoma of the stomach in accord with the developments in preparation, anesthesia, technique, and after-care. In a report by Parsons,¹⁴ from our clinic in 1933 and a later one in 1939¹⁰ on the curability of cancer of the stomach, we find the resectability increased from 27 to 37 per cent and the operative mortality reduced from 38 to 25 per cent. In these comparative groups, there was 20 per cent of five-year cures in the first series as compared to 21 per cent in the later. These figures include the operative mortality. Although it was disappointing to find no appreciable increase in the five-year cures, it was evident that a greater number of patients had more months of respite in the latter group than the former. In other words, we have been more bold in our attempts

than our predecessors and have actually accomplished more difficult and more extensive resections with a lower mortality rate, still we have no greater percentage of patients living over five years. The questions naturally arise: Is the effort expended justifiable and how can we obtain better results?

In the past eight years, more than 100 patients have been subjected to total gastrectomy for cancer by members of our staff. This includes several operations accomplished through the chest by members of the thoracic service. That immediate results have been poor and that respites in the survivors have often been of short duration, we admit. On the other hand, one patient is alive and apparently free of disease seven years after operation, and numerous others are still alive for shorter periods or have had respites of from one to nearly five years. Actually, in some of the most apparently unfavorable cases, there have been the best results. Although one may question the judgment in the selection of these cases and in the effort expended, we feel that there is no reason to lower our standards of perseverance in this otherwise hopeless group of individuals.

There is much to be said regarding the type of operation that must be considered in the more favorable group of patients. Ogilvie⁸ has pointed out that the nodal distribution in cancer of the stomach runs true to a pattern. One should include in the resection the great omentum, all the nodal area about the pylorus, and the cardia. This operation must be looked upon like radical operation for cancer of the breast or colon where it is clearly demonstrated that concomitant dissection of the available lymphatic extension increases the number of cures. Actually, the inclusion of these lymphatic areas contiguous with the stomach creates no problem if one takes it into consideration from the beginning of the operation. It is my belief that these areas should be included in the early cases of doubtful malignancy. By this means, we may materially increase the number of cures. If there is extension by contact to many structures, the outlook is poor; yet one can often include the spleen, transverse colon, a part of the pancreas, and even a segment of the liver in a justifiable attempt to remove all obvious disease. The thoracic surgeon has the best approach to those lesions involving the lower end of the esophagus and the lymph nodes in this region.

It is my opinion that the extent of operation should be increased rather than decreased. We have had the opportunity of removing the

proximal segment of the stomach for recurrence of disease following a subtotal resection done three years previously. The second operation gave a respite with comfort and ability to work for over a year. Could a cure have been obtained if a more extensive procedure had been done in the first place? There are types of cancer of the stomach that extend along the stomach wall in an insidious manner, so that often one is aware of cutting through probable extension at the time of subtotal gastrectomy. It is likely that I will be quoted as advocating total gastrectomy for cancer in all cases. This is not true, since I am sure that many of them can be resected without having any recurrence in the stomach segment. On the other hand, I think we should consider the added chance of eradicating all disease by total gastrectomy whenever we feel that the chance of cure can be justifiably increased thereby.

In total gastrectomy, one should expose an adequate 5 to 8 cm. of lower esophagus. This is always possible by dividing the vagus nerves. We have found that fixation of the jejunal loop to the diaphragm is of great aid in the anastomosis.¹⁵ We have adopted, with gratitude, the modification of anastomosis advocated by Graham¹⁶ which implants the esophagus into the anterior wall of the distal jejunal loop, and encloses this area by using the proximal loop of jejunum over it. This technique simplifies the operation tremendously and has entirely eliminated the problem of leakage at the anastomosis. We have had better results with bringing the jejunal loop through the transverse mesocolon. We have always made a large entero-enterostomy between these loops of jejunum. Recently, we have eliminated the need of the Levine tube postoperatively by placing a catheter in the jejunum for drainage of the salivary, biliary, and pancreatic secretions.¹⁷ A jejunostomy for feeding has always been used in our cases.

SUMMARY AND CONCLUSIONS

1. Benign and malignant lesions of the stomach are not always distinguishable.
2. Polyposis is probably always benign originally but malignant degeneration occurred in 41 per cent of our cases.
3. Leiomyomata may be locally excised only when small and in inaccessible regions of the stomach.
4. Ulcer of the stomach could not be distinguished from cancer in a number of our patients studied. The over-all diagnostic per-

centage error was 14.

5. Short duration of symptoms in the older age group and lesions located in the prepyloric and fundal areas were more often found to be malignant than benign.
6. Medical treatment of gastric ulcer is less effective than conservative measures for duodenal ulcer.
7. Radical surgery is less dangerous in gastric ulcer than the same type of operation for duodenal ulcer.
8. Cancer of the stomach is more curable in the early stages of the disease.
9. Operation should be done in all doubtful lesions of the stomach.
10. Attention must be given to a careful inclusion of the lymphatic spread in the operative attempts to cure cancer of the stomach.

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DISORDERS OF THE DIGESTIVE SYSTEM LEADING TO VITAMIN DEFICIENCY STATES IN INFANTS AND CHILDREN*

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IN times like these the importance of the vitamins in clinical medicine needs no stressing. We are on the lookout for deficiency states which are imposed upon a community through famine, and for those which derive from ignorance of the distribution in natural foods of the essential food factors or from misapprehension of their susceptibility to destruction. In addition to these two main groups, the deficiencies, based on inaccessibility of supply and those due to faulty understanding of the requirements, there is a third great class, the deficiencies which are secondary to disorders of the digestive system and which develop because the vitamins are not adequately absorbed or, if absorbed, are not properly utilized within the body. It is this last group on which I should like to focus attention.

Let me cite two examples. As many as ten years ago it was well known by pathologists¹ that histologic lesions pathognomonic of vitamin A deficiency were found at times in patients presenting the characteristic picture of pancreatic fibrosis. For a long time it was not clear which was the primary lesion, which one was secondary. Gradually, in the course of years, an imposing mass of circumstantial evidence was accumulated which left little doubt that the pancreatic impairment occurred first, that this then led to a disorder of pancreatic function in digestion, and that faulty assimilation of vitamin A must be regarded as a later result—that is, as a consequence and not a cause.^{2,3} This concept has in the course of time been amply fortified by the results of its clinical application: in many patients in whom it has been possible to establish during life an unquestionable diagnosis of pancreatic deficiency, proper augmentation of the daily intake of vitamin A has

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brought about a regression of both clinical and laboratory evidences of vitamin A deficiency, even though pancreatic exocrine function has remained at zero level over a period of years.

A second example has to do with a deficiency of prothrombin formation secondary to acquired hepatic disease. At the age of seven months a female infant suffered a severe febrile illness accompanied by jaundice and enlargement of the liver. The fever and other acute symptoms subsided in the course of a few days, but jaundice and hepatomegaly persisted, along with some loss of appetite, generalized itching, and the passage from time to time of pale stools. A year or so following the original attack of jaundice, a bleeding tendency expressed itself in numerous ecchymoses which followed minor injuries and in prolonged bleeding from scratch marks inflicted on herself by the child in the effort to find relief from constant pruritus; heaped-up, black crusts formed in various parts of the body, especially on the ears. The bleeding time was slightly prolonged, the coagulation time moderately so. Vitamin K—that is, menadione—was administered by mouth in dosage of one milligram daily, with prompt and satisfactory relief of the bleeding tendency and reduction of the prothrombin time from forty-five seconds to a normal level of twenty-six seconds. The patient was eventually shown to have an acquired cirrhosis of the liver on an infectious basis, of which she finally died.

Both of these examples illustrate the influence of clear-cut lesions of organs of digestion in producing impaired absorption of vitamins, in the cited cases vitamins A and K, both of which are lipoid-soluble substances. This brings up a practical point. The early classification of essential food factors in two groups, the fat-soluble and the water-soluble types, fell into the discard to some extent as individual vitamins were identified; but from the point of view of the physiology of food absorption there is eminent reason for reviving this older grouping. Certainly we see numerous instances in which more than one deficiency syndrome within the fat-soluble group occurs in an individual patient; and likewise, though perhaps less commonly, a single subject will be found who presents evidence of impaired retention of several of the water-soluble factors.

Taking up the fat-soluble vitamins first, we find the ones most firmly tied up to defective absorption to be A and K. Clinically, such deficiencies are seen in conditions in which there is a disturbance of

the absorption of food fat—in diseases of the liver and bile ducts which impair the production and excretion of bile, in conditions which lead to inadequate delivery of pancreatic enzymes into the intestinal lumen, rarely in conditions which directly affect the mucous membrane of the digestive tube at the site of fat absorption and interfere with the transfer of lipoids through the gut wall. It is significant that though none of the vitamins is a true fat, their absorption from the chyme parallels closely the efficiency of absorption of food fat; and also that the provitamins, which in some instances—as in the case of vitamin K—may be numerous and chemically somewhat diverse, suffer for practical purposes the same physiological fate as the preformed vitamin.

The kind of clinical situation to which I am referring is of course one in which the principal symptoms are due to the underlying disorder of some part of the digestive system, and in which the evidences of vitamin deficiency creep in so insidiously that they often are not perceived until perhaps too late for regression or repair to be achieved. The whole point is that a great deal can be done to sustain the patient while the struggle against the fundamental disease is going on, provided these incidental risks are kept in mind.

Lesions or functional disorders of the liver, of the pancreas and of the intestinal wall have been mentioned. Some elaboration of these three general themes is in order.

In pediatric practice we look for evidences of faulty absorption of fat-soluble vitamins in congenital atresia or defective development of the bile passages, in obstructive jaundice of any acquired form, usually secondary to some type of infectious cirrhosis, or in acquired obstruction of the common bile duct—the last a decidedly rare event. To be properly forewarned it is enough to know that the patient is deeply jaundiced, has pale stools, and has a high level of serum bilirubin with a large fraction of it giving the direct van den Bergh test. Additional confirmation of the hazard which confronts the patient may be obtained by the simple and quantitatively crude test of fat absorption based on microscopic examination of a stool sample, using Scarlet Red as a fat stain. With a little experience gained from applying this test to a few normal and pathological stools one can soon gauge the fat content of a given sample on a 0 to ++++ basis with sufficient accuracy to identify reliably the patient whose defect of fat absorption calls for special protective measures.

Of the disorders which reflect primarily a deficiency of the external secretion of the pancreas, the classical example is congenital pancreatic fibrosis. In spite of the emphasis which pediatric thought and writing have put on this disease in the past five years, its importance remains incompletely recognized. From the data of two large pediatric hospitals, the Infants' and Children's Hospital in Boston and the Babies Hospital in New York, the frequency of some degree of pancreatic fibrosis is computed at something near 275 instances among 3400 unselected autopsies, or a rate of 8 per cent among fatal cases of disease of all types. Fibrosis of a severity which suggested from its morphology that the exocrine function of the pancreas had been essentially lost during life occurred in about 1.5 to 3 per cent. Dorothy Andersen's clinical and pathological studies have provided ample warning that pancreatic insufficiency makes itself known under a variety of symptomatic guises: in earliest infancy it is the underlying cause of a variety of intestinal obstruction in the newborn, the so-called meconium ileus; in the next age period, from the age of a week or so to the end of the first six months of life, it provides the background for retarded growth and development or for chronic bronchitis, sometimes with bronchiectasis and pneumonitis; and later, from the age of six months on, it appears under the mask of the celiac syndrome. Accurate diagnosis during life depends on the demonstration, by the application of biophysical and biochemical methods, of absence of the normal pancreatic enzymes from duodenal contents aspirated under controlled conditions. The absence or virtual zero level of trypsin is particularly significant. However, the simple test of stool examination for unabsorbed fat as just described serves a useful purpose as a screening test; for if the patient while on an average diet, in particular, a diet containing fat in customary amounts, shows by this test that he is able to absorb ingested fats to a normal degree, the diagnosis of pancreatic insufficiency is untenable and the more refined and technically more difficult evaluation of duodenal enzyme concentrations may safely be dispensed with. If, on the other hand, the stool fat test demonstrates a significant degree of impaired fat absorption, one must be prepared to go ahead with the procedures which lead to a more certain appraisal of pancreatic performance.

Disorders which have their focus in the intestine itself, and which may lead to defective absorption of fat-soluble vitamins, are not so

well documented by anatomical studies as are those of the liver and pancreas just described. The commonest form is true celiac disease. In this disorder the concentrations of enzymes in the duodenal juice are normal, or nearly so. Faulty absorption of fat is nevertheless an outstanding clinical feature and one which lends itself to quantitative verification by a number of laboratory determinations. Although it is only in the most severe cases that the intestinal wall shows changes of a degree that renders poor fat absorption readily comprehensible, the evidence of a profound functional alteration in digestion and absorption of fat is so clear in all cases worthy of this diagnosis that there is little reason to doubt that the primary disturbance responsible for the syndrome lies within the intestinal mucosa. When the disease is out of hand, when the patient is having a bout of diarrhea and passes numerous bulky stools containing a high concentration of lipids, the risk of clinically significant deficiency of fat-soluble vitamins becomes obvious.

Now what do such threats add up to in terms of the individual vitamins of this fat-soluble group? Experience tells us that, so far as morphological changes are concerned, A-deficiency occurs more commonly in the pancreatic disorders than in those of liver or intestine. Ample warning has been obtained from the pathological studies of fatal cases, so many of which have exhibited the microscopic lesions of a lack of vitamin A in the epithelium of the trachea and bronchi, the conjunctiva, the urinary tract, and in many of the ducts communicating with the alimentary tube. Biochemical studies during life confirm the frequency of deficiency of the fat-soluble group. The concentration of vitamin A in the circulating blood is low, and this is rightly believed to correlate closely with the state of the body stores. Abnormalities also occur in the shape of the vitamin A absorption curve, plotted on the basis of a number of blood level determinations made following the oral administration of a generous loading dose.⁴ These last-mentioned observations point the way to successful prophylaxis and therapy, for seldom does one encounter a patient whose blood vitamin A curve does not exhibit some degree of rise in response to the test dose; and consequently one needs only to make certain that the small quantity of fat which gains admission to the body from food supplies shall be accompanied by a rich dietary supply of vitamin A or carotene, or possibly both. Parenteral administration, generally unsatisfactory in

actual practice, is fortunately not needed. In one of our severe and ultimately fatal cases of congenital fibrosis of the pancreas a marked degree of xerophthalmia which was present at the time the child was first examined responded satisfactorily to the oral administration of halibut liver oil, so satisfactorily, indeed, that the eyes had become almost healed at the end of a month. Direct observations of this kind support the hypothesis that the bronchitic and bronchiectatic symptoms which form such a conspicuous part of the symptomatology of pancreatic fibrosis during the first year of life may well represent a deficiency of fat-soluble vitamins, for they often regress markedly when the dose of A and D concentrates is raised to a high level.

The risk of vitamin K deficiency in obstructive jaundice has received so much attention from surgeons that the need for prophylaxis is not liable to be forgotten, even when immediate surgical intervention is not contemplated. Clinically manifest K deficiency seems to occur more frequently in association with hepatic disease than in disorders of pancreatic or intestinal function, possibly because of the part played by bile salts in promoting normal absorption of the vitamin during health. On the basis of actual experience it is hardly to be feared that great harm will be done, or irreparable damage caused, if prophylaxis happens to be omitted up to the point at which the occurrence of superficial hemorrhages or the observation of a prolonged coagulation mechanism brings the need forcibly to mind. In this respect there is no comparison between the seriousness of the potentialities as regards deficiency of K and deficiency of A; the latter is vastly more ominous. Concerning the practical question of how to overcome the deficiency of vitamin K in the presence of impaired absorption of food fat, it is a good working rule that the simplest method which will work is the best one to adopt. Oral administration of some preparation of menadione in dosage of two or three milligrams daily is usually effective, and once saturation has been achieved the dose can safely be dropped to one milligram a day. Although parenteral administration is feasible, it seems to be seldom necessary.

The chance of vitamin D deficiency is not so great as might be supposed. Although the absorption of vitamin D from the diet runs parallel with the efficiency of fat absorption in general, its action in preventing rickets is not in urgent demand when the rate of bone growth has dropped nearly if not quite to the vanishing point, as is

the case in the serious digestive disorders included in this discussion. It is generally recognized that we see in this country far less celiac rickets than is the rule in England, a difference in incidence which may well be due to the prevailing tendency on this side of the Atlantic to supply vitamin D more liberally as a matter of general routine in the care of infants and young children. When clinical recovery from celiac disease sets in, and when the patient begins not only to gain in weight but to grow in stature, then generous administration of calciferol or an equivalent form of D becomes imperative. This applies not only to patients with true celiac disease or idiopathic steatorrhea but also to patients with pancreatic fibrosis and those with obstructive jaundice.

The other fat-soluble vitamins must be passed over in silence for want of evidence.

Turning now to the water-soluble group, for practical purposes ascorbic acid and the various members of the B complex, we realize that they have this much in common, that they can all be shown to be adequately absorbed in all but the most severe grades of disorder of the digestive organs, but that their retention and their proper utilization in enzyme reactions in metabolic processes cannot be taken for granted. Into this deep pit of ignorance only the faintest blush of light has penetrated. We know that any individual who suffers from diarrhea is liable to be in negative balance with regard to thiamin⁵ and ascorbic acid;⁶ and many of the patients with the disorders referred to are subject occasionally to attacks of diarrhea. Other circumstances such as increased metabolism,⁷ high environmental temperature,⁸ infection⁹ and parenteral administration of large volumes of fluid,¹⁰ any of which may affect these patients in more or less close causal relationship to the underlying disease, have been shown to deplete the stores of one or more of the water-soluble vitamins. Hence, it behooves us to be forewarned and to weigh these potential risks in setting up the program of treatment. The close dependence of normal carbohydrate metabolism on an adequate supply of thiamin emphasizes the special need for that vitamin on the part of patients who, because their absorption of fat is impaired, must derive a large fraction of their energy from carbohydrate.¹¹

Therapeutic experiments, many of them admittedly crude in design, have disclosed the rough outlines of some of the physiological principles involved. It is appreciated that the lack of appetite which

accompanies some of these primary disorders of the digestive system may reflect a deficiency of any one of the water-soluble vitamins, and that one cannot trust the patient's appetite to indicate which vitamin or which several vitamins he stands in need of. There is evidence too^{12, 13} that some of the water-soluble vitamins play a part in the absorption of dietary fat and thus are concerned in the prevention of deficiencies within the fat-soluble group. Therefore we must resort, at first at least, to parenteral administration and at levels of dosage which will leave no doubt that the needs are covered. The choice of dosage levels must be arbitrary; fortunately there is no demonstrable danger in the case of ascorbic acid if one gives day after day ten or even twenty times the normal daily maintenance requirement. With respect to the components of the B complex, it has been shown that a proper balance must be maintained;¹⁴ if, for example, too much thiamin is given in relation to the intake of niacin, a borderline deficiency of niacin may suddenly express itself in symptoms.¹⁵ Therefore, to avoid this sort of therapeutic ataxia it is wise to employ crude liver extracts, in which the components of the B family occur in proportions which are related to some biological base line, in this case healthy animal tissue, rather than to the arbitrary whim of a compounder of mixtures.¹⁶ When the time comes for a shift from parenteral to oral administration, a preparation made from natural yeast has comparable advantages.

The proof of the pudding is in the eating, and the justification for belaboring at some length the peculiar nutritional needs of patients with serious disorders of the digestive system lies in the satisfactory record which some of them, even some of the worst of them, have achieved over a period of years not only from the standpoint of general growth and development but also by the criteria of avoidance of repeated infections and attainment of a cheerful attitude of mind. A few of the patients with pancreatic fibrosis whose fundamental problem happened to be recognized before irreversible secondary changes in other structures and functions had set in have already enjoyed a life span far greater than had originally been forecast, and continue to return for follow-up visits in a state of health which allows one to hope that this state of affairs will persist. It is impossible to avoid the conclusion that credit must go in no small part to the prophylactic program sketched out, which aims to suppress by-effects of the underlying disturbance even when the latter is beyond the reach of direct

attack. The program itself, while comprehensive in scope, is neither onerous nor elaborate. It merely recognizes that the avoidance of deficiency states in patients with impaired digestion calls for dosage levels of vitamins which for a normal subject would be unnecessarily high and ordinarily quite unjustifiable.

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THE PRESENT STATUS OF ULCERATIVE COLITIS AND REGIONAL ENTERITIS*

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WITH the accumulation of experience and the improvement of diagnostic criteria, it has become more and more evident that there are many forms of ulcerative enteritis. All forms of ulcerative enteritis assume in their very nature the status of chronic disease. Hence, the terms "chronic ulcerative colitis" and "regional enteritis" are best used to denote general clinicopathologic syndromes, rather than to designate one of the several specific disease entities in which these syndromes are present.

In medical practice it becomes necessary to study chronic ulcerative colitis and enteritis according to etiologic types, and the first and most fundamental clinical effort should be directed at determining the specific etiologic factor responsible for the development of the syndrome in a given case. The infection may be caused by one or more of several bacteria or animal parasites, in association with certain dietary and constitutional deficiencies, or by other and some still unknown conditions.

We now recognize a variety of inflammatory intestinal conditions. Some of them are strictly localized to the large intestine, others to the small and still others may involve both small and large intestine. It is well, always, to keep this in mind when studying a given case. The concept, advanced by a few, that ulcerative colitis and regional enteritis are all "of a piece" is, in the light of present knowledge, no longer tenable. One must rather think in terms of many disease entities, each having this or that cause with these or those pathologic features and in turn clinical manifestations. If these facts are kept in mind a more rational treatment may be instituted.

TYPES OF COLITIS AND ENTERITIS

Strictly speaking, all forms of colitis, ileitis and jejunitis are forms

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of enteritis. However, by common usage the tendency of referring the term enteritis to the inflammations of the small intestine has developed. It is well understood, however, that some forms of ulcerative colitis, although primarily inflammations of the large intestine, may advance orad to involve the distal segments of the small intestine. So also may some primary inflammations of the small intestine advance caudad to involve the large intestine. For practical purposes, however, it is best to discuss separately (1) the lesions primarily confined to the large intestine, (2) those primarily confined to the small intestine and (3) those regional inflammatory conditions which have, in their very nature, a tendency to spread to involve both small and large intestine.

Streptococcal ulcerative colitis: The most common condition of the group involving primarily the large intestine is that commonly referred to as "nonspecific" or "idiopathic" ulcerative colitis. If physicians using the term would apply it to a single disease entity, well and good, but unfortunately a variety of ulcerative intestinal conditions are included under this designation. In fact, some writers include under it all cases of ulcerative colitis which are not of amebic or tuberculous origin. Consequently, the term becomes no longer tenable. The terms "colitis gravis" and "thrombo-ulcerative colitis" are descriptive of the serious nature of the disease and its pathologic inception, and go far in depicting a disease entity. However, since in this discussion I shall aim to give definite status to each form of ulcerative enteritis, I shall refer to this type as streptococcal ulcerative colitis.

This disease has characteristic pathologic manifestations, and hence typical proctoscopic and roentgenologic features. Its lesions begin in the most distal segment of the rectum, just above the anal canal. Diffuseness of involvement of the bowel is its pathognomonic feature. Whether 1 inch (2.5 cm.) of the lower part of the rectum or 5 feet (1.5 meters) of bowel are involved, the involved segment always is affected in its entirety, its entire circumference and the deeper layers of the wall and the mucosa secondarily. This gives the granular, easily bleeding mucous membrane so characteristic of this lesion. The disease tends to spread upward until the entire colon, and even the lower part of the ileum in the late stages of the disease, become involved. Since it is primarily a disease of the intestinal wall, a very characteristic roentgenologic picture develops. The bowel becomes diffusely narrowed, haustral markings are erased, the flexures and curves become more

angulated and the result is a smooth tube. In this, streptococcal ulcerative colitis differs from all other forms of ulcerative intestinal disease, except perhaps regional enteritis when it is confined to the distal portion of the ileum. The latter condition has, however, many features to distinguish it from streptococcal ulcerative colitis. Because of the relatively high incidence of the streptococcal form of ulcerative colitis, and because of the consistency with which its clinical, proctoscopic and roentgenologic manifestations conform to a certain pattern, I am inclined to use this type of ulcerative colitis as a norm and to describe other types chiefly by noting in what respects they differ from it.

This form of ulcerative colitis manifests itself in a variety of ways but in general the clinical manifestations follow one of three general courses. When the lesions are limited to the lower segments of the large intestine, particularly the rectum and rectosigmoid, the onset of symptoms can be described as insidious. The patient may have normal motions of the bowel but in addition may pass two or three or many bloody, purulent rectal discharges. He may not have any other important systemic symptoms except that he will gradually begin to speak of not feeling well. His complaint of not feeling up to par may increase gradually as the number of rectal discharges increases and ultimately a mild form of diarrhea may develop.

The second common onset may be classified by saying that the symptoms are severe. The patient may start rather suddenly with bloody diarrhea, low gradual fever, gradual loss of appetite and with them loss of weight and all the concomitants of a moderately severe illness. All the symptoms may start in a fulminating manner with an onset almost like that of lobar pneumonia or other similar serious illness. There will be a high fever, massive discharges of bloody material from the rectum, great prostration and rapid depletion.

A patient's symptoms may remain in the insidious form for months and years and then at the time of an infection of the upper part of the respiratory tract, some other intercurrent illness or perhaps some severe nervous trauma, there may be a sudden exacerbation of the disease and a change to a severe or even the fulminating form. The question is often raised whether these are different diseases or stages of the same disease. Experience seems to indicate that these are stages of the same disease attacking patients in various ways. Thus, one must be ever on the alert for the occurrence of this disease in these several forms so

that it may be distinguished carefully from the types of colitis which are to be discussed presently.

Amebic ulcerative colitis: Another type of colitis in which the lesions are limited to the large intestine is that caused by *Endamoeba histolytica*. Here the lesions are localized primarily to the cecum and possibly the flexures of the large intestine, although the entire large intestine may be involved. If the disease has advanced sufficiently toward the rectum so that lesions are visible in its mucous membrane, they present a very characteristic appearance. The ulcers give the impression of being punched out, with raised edges covered by a fleck of mucus and a hyperemic zone around the individual ulcer. Between the ulcers the mucous membrane is relatively normal. The disease largely affects the mucosa instead of the wall and there should be little difficulty in distinguishing this type of ulcerative colitis from the streptococcal variety of ulcerative colitis. Its extension is exactly opposite to that of the latter. Its lesions start in the cecum and spread caudad instead of starting in the rectum and spreading orad as do those of the streptococcal variety of colitis. Consequently, the symptoms are quite at variance to those of the streptococcal variety. Bleeding occurs relatively late in the disease instead of being present as one of the first symptoms. The severe prostration of the fulminating type of ulcerative colitis is observed rarely. The patient is usually in a relatively good condition. Roentgenologic examinations, too, show a rather characteristic deformity of the large intestine when the disease is sufficiently advanced. However, even early in the disease there may be the characteristic features in the cecum: namely, some narrowing and irritability when no other colonic lesions exist. With the progress of the disease the cecum becomes coned or narrowed to a point and the entire ascending colon may be narrowed irregularly. This is not a smooth diffuse narrowing such as one sees in the streptococcal type of ulcerative colitis. As the rectum is approached, there will be less and less roentgenologic evidence of disease except in those cases in which the greatest disease is at the flexures or in unusual segments.

Ulcerative colitis due to the virus of venereal lymphogranuloma: A third form of ulcerative colitis in which the lesions are limited to the large intestine is that caused by the virus of venereal lymphogranuloma. Here again the lesions start in the rectum and distal segments of the large intestine. The disease is also of the wall of the bowel but involves

not only the wall but the lymphatic structures around it and so there develops a condition in which a stiff tube having the feel and giving obviously the appearance through the proctoscope of perirectal inflammation exists. There may be multiple small sinuses from the mucous membrane to the deeper structures and so a rather definite proctoscopic and roentgenologic picture results. The disease will be limited to the rectum and rectosigmoid structures and the normal bowel will be reached much more abruptly than in the streptococcal variety. Almost invariably the patient will feel generally well and his complaints will be largely in reference to the local rectal condition. The diagnosis in this type of case will depend largely on the history of previous venereal infection, possibly the presence of buboes and among women very commonly the presence of preceding vulval lesions. The Frei reaction will be positive. But even if these conditions exist, the diagnosis of colitis due to the virus of venereal lymphogranuloma is not tenable if characteristic lesions of the rectum do not exist.

Regional ulcerative colitis: The fourth type of ulcerative colitis in which the lesions are limited to the large intestine is one of which the cause is not clear. We speak of it as a regional type of ulcerative colitis. The lesions involve isolated segments of intestine and may involve any segment, much in the manner of regional ileitis except that here the site of the disease is the colon. The lesion may be subacute or chronic and usually is quite destructive but also there may be evidence of hyperplastic changes. Commonly segments of the intestine from 6 to 12 inches (15 to 30 cm.) long are found to be involved with perfectly normal bowel distal and proximal to the lesion and always the rectum is not involved. In other words, this segmental type of colitis involves regions of the large intestine above the view of the sigmoidoscope. The wall of the involved segment is *also* stiff and thickened but the involvement is not as diffuse, regular and smooth as in the streptococcal type of ulcerative colitis. Thus, the roentgenologic examination is the most important objective method of establishing a diagnosis. Usually such a regional type of colitis remains localized to a segment of large intestine for months and years. Very occasionally, however, it has been known to spread orad and caudad so that ultimately even the distal portion of the ileum has become involved. The latter has initiated a difficult situation, indeed, and has always brought up the question whether this and so-called regional ileitis may not be the same or closely related condi-

tions. However, the fact that the condition usually remains localized to the large intestine, whereas regional ileitis commonly spreads from the ileum proximad to involve the jejunum and distad to involve the cecum and ascending colon, raises a very definite question of their being separate entities.

Regional ileitis: The two conditions commonly starting and having a tendency toward being confined to the small intestine are regional ileitis and intestinal tuberculosis. Both of them, if they are separate entities, are inclined to remain localized to the small intestine. In both of them, the infection is inclined to spread orad and caudad, thus ultimately involving parts of the large intestine and particularly the ileocecal coil. Thus, for the first condition the term "regional ileitis" becomes particularly suitable. When one speaks of this, one is referring to a subacute or chronic, destructive, exudative and proliferative regional inflammatory process commonly and perhaps usually beginning in the distal portion of the ileum. The name now refers to a definite disease entity well described by Crohn, Ginzburg and Oppenheimer¹ in 1932. In many respects the onset and clinical course of this condition are similar to those observed in the cases of regional colitis. However, patients suffering from the latter condition are prone to be much sicker than those who have regional ileitis. The onset of the disease is usually insidious but by the time medical aid is sought, well pronounced features of advanced disease are frequently apparent and the diagnosis can be readily established.

As with so many chronic infections of a proliferative and destructive nature, the story frequently begins with the complaint of fatigue, general malaise and loss of weight. Associated with these symptoms, or soon after their onset, a patient will complain of a mild, usually intermittent, type of diarrhea. The stools will be loose and watery, and defecation will be associated with cramps. Periods in which normal or even hard, dry stools are passed may alternate with diarrhea. The story in these respects is similar to that of a patient who has intestinal tuberculosis. As a rule, however, in cases of regional ileitis, progression to the next phase is more rapid and symptoms are more severe than in cases of intestinal tuberculosis. In the former, attacks of abdominal pain supervene and the pain may be of the dyspeptic or obstructive type from the first. In either event, obstructive features will soon predominate.

Generally speaking, there are four phases of the disease. The earliest

manifestation is that of an acute inflammatory process. As the terminal portion of ileum is the most frequent initial site of the disease, irritation of this portion of the intestine and its adjacent peritoneal covering produces a picture difficult to distinguish from acute appendicitis. The most common symptoms are fever of low grade, leukocytosis, nausea, vomiting, and tenderness and pain in the epigastrium or right lower abdominal quadrant. Diarrhea and cramps are unusual at this stage of the process.

As the disease advances, intermittent attacks of diarrhea are characteristic. The typical syndrome of enteritis of low grade then prevails, for the patient has fever, anemia and a palpable mass in the right lower abdominal quadrant and has lost weight; his stools are loose or watery and if any pain is present it is mild and colicky.

Remission of symptoms is common in the two stages described, but as the stenosing effects of the disease increase, the periods of relief are shorter and occur less frequently. The symptoms typical of intestinal obstruction are superimposed on those of chronic enteritis. The attacks of diarrhea are more profound and are accompanied by severe abdominal cramps, borborygmus, abdominal distention or visible contracture of the coils of the small intestine proximal to the diseased segment. Malnutrition and anemia become prominent features since much of the nourishment and fluids is lost because of the diarrhea. Furthermore, intake may be greatly limited on account of persistent nausea or even vomiting.

The fourth and final phase of the disease is attained when either acute obstruction is superimposed on the chronic condition or perforation of the bowel occurs and there ensues the formation of an abscess or fistula. The fistula may communicate with an adjacent portion of the intestine, with other viscera or with the abdominal parietes. The debility occasioned by the sepsis and deprivation of nutritional elements and fluids assumes great significance and in itself may be the terminating factor.

The course of regional enteritis as delineated is uniform only in a very general way. In the individual case the first signal of impending trouble may be the onset of the syndrome of the late phases, or the symptoms may have progressed from an occasional episode of pain in the right lower abdominal quadrant or the epigastrium to intestinal occlusion, although there may have been little intervening disturbance.

In an occasional case the chief complaint will be the one which is only remotely associated with the malady.

These facts and others to be mentioned concerning the pathologic changes of the diseased segment of bowel give further evidence of the destructive, proliferative and progressive nature of the disease. Generally speaking, when one first sees these patients the disease is in the advanced stage and the pathologic process already has produced unmistakable gross deformity. There is evidence of attempted fibrotic repair associated with chronic inflammation on which acute exacerbations of the disease have been superimposed. Pathologic descriptions of the condition have been comparatively uniform. The terminal portion of ileum, as has been indicated repeatedly, is the segment most frequently involved. Thickening of the wall of the bowel, narrowing of the lumen of the bowel and ulceration of the mucosa with the formation of pseudopolyps are noted. These associated characteristics have been described often as granulomatous ileitis. The character of the lesions may range from subacute to chronic. At times the intestinal wall is greatly thickened by edematous infiltration. Pseudotubercles, in association with large foreign body giant cells, are common. Perforation with the formation of an abscess is fairly common. As a result of this, multiple communicating fistulas may develop. These are the result of chronic perforation which takes place so slowly that time is allowed for segregation of the process from the peritoneal cavity and usually small walled-off abscesses form. These, in turn, discharge their content into a neighboring viscus. Grossly, the most striking features are typical enlargement and loss of flexibility of the affected segment of bowel and shortening and great thickening of the mesentery, in which the regional lymph nodes are large and firm. The tissues have a dusky, bluish red appearance and a phlegmonous exudate is distributed over the serosal surface of the intestine.

In the instances in which the condition is of long standing, many exacerbations usually have occurred and a large phlegmonous mass may have resulted. It is often very difficult to separate such a mass from the surrounding structures. At times, too, such lesions may affect the bowel in segmental fashion with relatively normal uninvolved segments lying between the involved portions. The involved segments are readily distinguishable from the normal portions by their loss of elasticity and soggy hose-like appearance. The microscopic appearance of the lesion

does not have any characteristics which distinguish it from other chronic inflammatory processes. Cells of the lymphoid series appear to predominate, except in the earlier, more acute stages. In the chronic process, the small lymphocyte, plasma cell and fibroblastic elements are in the ascendancy; eosinophils may be present. Submucous lymphoid follicles are usually very numerous. Giant cells are encountered frequently and often contain crystalline or lipid particles. Focal collections of lymphocytes under the serosa with the giant cells here and there make the picture simulate tuberculosis.

Tuberculous ileocolitis: Another type of enteritis attacking primarily the small intestine is that due to *Mycobacterium tuberculosis*. The disease may be of the nature of extensive enteritis involving stretches of the intestine with rather normal segments of bowel between. The ulcers will be distributed irregularly and associated with lesions visible on the serous surface of the bowel and with miliary tubercles. The most extensive lesions will usually be in the distal segment of the small intestine and may extend to involve the cecum and other segments of the large intestine. This infection commonly attacks the ileocecal coil and it is at this point that the disease has its greatest activity. Only in the late stages will the lesions progress sufficiently caudad to be visible through the sigmoidoscope. Thus, the roentgenologic features will show characteristic irritability with rapid emptying and filling of the ileocecal region and great irregularity of the intestinal lesions will be observed in the roentgenogram. The smooth contour of the intestinal wall so commonly seen in the streptococcal type of colitis is not present in tuberculous ileocolitis. The disease again involves the mucosa more than the wall.

Other intestinal conditions: Other intestinal conditions which may or may not be of the nature of inflammatory disease are the following: (1) chronic bacillary dysentery; (2) ulcerative colitis of unknown cause (for those who still cling to the term nonspecific or idiopathic, the term might be applied to this group of cases); (3) a deficiency syndrome; (4) so-called allergic colitis.

There is a form of ulcerative ileocolitis which follows in the wake of severe bacillary dysentery due to one or several of the strains of *Shigella paradysenteriae*. Penner and Bernheim² have shown recently that the lesions of bacillary dysentery are in the nature of toxic reactions mediated through a sympathotonic reaction. This might explain

the fact that the lesions are also irregular and disseminated. In the occasional case in which extensive destructive ulcerative disease occurs, secondary invaders may be responsible for the late lesions. When lesions are visible through the sigmoidoscope, their irregularity as far as size, extent and mucosal appearance are concerned is particularly striking. It has been said that they are characteristic because of their irregular and yet extensive distribution. The same impression is gained from the roentgenologic appearance of the bowel in these cases. Still, the diagnosis will depend largely on the presence in the blood of agglutinins (in significant titer) of one or several strains of *Shigella paradysenteriae*.

One is particularly impressed with the latter fact when encountering cases of ulcerative ileocolitis belonging to the group which I have designated as of unknown cause. Here again the ulcerative disease may be extensive, involving long stretches of small and large intestine, or it may involve only the rectum and sigmoid. Whatever segment is involved, the appearance of the lesions is at variance with those of the conditions described having a specific cause and strikingly at variance with the appearance of the bowel in the streptococcal variety of ulcerative colitis. Agglutination of *Shigella paradysenteriae* will be absent. Culture made from the lesions and examinations of the stools will not be diagnostic. The lesions will be distributed irregularly and tend to resemble those of amebiasis or tuberculosis. Yet, usually one will detect differences. The differences are sometimes hard to describe, and it has been said that the ulcers are characteristic by being so uncharacteristic. The same thing will hold true as far as the roentgenologic examination is concerned. This is the group of cases that will particularly tax the physician's ingenuity and the response to one form of therapy or another will often be minimal. In these cases, too then, surgical intervention will more often be employed.

The type of intestinal disorder of the nature of a deficiency syndrome, other than sprue and pellagra, should actually not be discussed here. It is brought up only because there are still some who feel that the deficiency state plays a primary role in some of the types of ulcerative colitis which have been discussed. The history of patients suffering from an intestinal disorder in which a food deficiency is important is usually characteristic. Such persons may have gone for months and years on an inadequate dietary regimen. The result may be atrophy of

the intestinal wall. The appearance of the bowel through the sigmoidoscope may suggest diffuse hyperemia. No real ulcers will be present. The roentgenogram may show dilatation of the large intestine with minimal changes of the mucosal pattern in the form of what appears to be a "fuzziness" of the mucous membrane and in the small intestine a typical pattern of barium puddling and segmentation will be observed.

What has been said about the deficiency syndrome affecting the intestine might also be applied to so-called allergic colitis. Everyone will accept the fact that there are patients who exhibit symptoms of intestinal allergy. Few will be impressed by the thought that such allergy is a primary factor in ulcerative intestinal disease. It seems obvious that occasionally in severe cases of intestinal allergy, mucosal abrasions may occur so that ulcers of a transient nature may be present. There is, however, little or no evidence available that these form the basis of a type of ulcerative colitis. It would seem better to consider intestinal allergy as a condition quite apart from the big problem of ulcerative enterocolitis, in the realization that it may play a part in many ulcerative intestinal inflammations but that it is not necessarily causative in any of them.

CONCLUSIONS

This discussion emphasizes the fact that there are many varieties of ulcerative enterocolitis. One cannot emphasize too strongly the importance of establishing as nearly as possible the nature and cause of a given case. Each type recognized to date has some characteristic features which set it apart from the others. In the streptococcal variety, the diffuseness of involvement and the typical proctoscopic and roentgenologic pictures together with the finding of the streptococcus are important. In the amebic, the finding of *Endamoeba histolytica* is of the greatest importance. In tuberculous colitis, the presence of *Mycobacterium tuberculosis*, together with the history and finding of tuberculosis elsewhere, is of great value. In the cases due to *Shigella paradysenteriae*, significant agglutinin titer of the blood serum is significant. In the cases due to the virus of venereal lymphogranuloma, the positive Frei reaction and the characteristic appearance of the lesions are essential. In the regional types and the groups still of unknown cause, continued and careful study is essential. It is important that these be not

confused with those forms of ulcerative colitis of specific cause and characteristic features.

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THE BASIS OF A CLASSIFICATION OF DISORDERS FROM THE PSYCHOSOMATIC STANDPOINT*

LAWRENCE S. KUBIE

I. INTRODUCTION

THE psychiatrist who works in a general hospital is consulted by his colleagues on a wide variety of problems. His assistance is sought in differential diagnoses, in treatment, and with increasing frequency in joint research on the interrelationship between psychological and physiological levels in the body's experience, as this interrelationship influences the course of some specific disorder.

It is not strange that in the effort to characterize widely different psychosomatic relationships, a host of terms has come into use, such as: conversion symptoms, hysteria, body reference, body representation, somatic compliance, organ inferiority, constitutional inadequacy, patho-neurosis, organ neurosis, actual neurosis, neurasthenia, sexual neurasthenia, hypochondriasis, hypochondriac, chronic invalidism. These terms have no constant usage. Their meanings overlap, their implications vary, and they fail to characterize the nature of the psychosomatic interrelationships which it is their purpose to indicate. It is this situation which has instigated the present effort to bring some systematic order into this chaos, by arranging the phenomena in groups which have logical, physiological, and psychological implications.

II. BASIC TYPES OF PSYCHOSOMATIC RELATIONSHIP

Two fundamental categories of psychosomatic relationship are recognizable: to wit, susceptibility, and somatization.

A. SUSCEPTIBILITY

Susceptibility includes the differential susceptibilities of different morphological, physiological, and psychological types to different dis-

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eases. This ancient and honorable field of medicine disappeared from medical studies for many years, only to reappear recently in the studies of physiological and morphological types by Kretschmer,¹ Draper,² Wertheimer and Hesketh,³ Sheldon,⁴ and others. The reawakening interest in the correlation between psychological types and such physical diseases as arthritis, various kinds of heart diseases, diabetes, and even the proneness to accidents, is due almost entirely to the pioneer work of Dunbar and her associates.⁵

The present study of classification will not attempt to include the field of *Susceptibility*, because it is a phase of the problem which can best be analyzed by those who have been working directly with it.

B. SOMATIZATION

The Stages of Dissociation:

Somatization is proposed as a general term for any process by which tensions which are generated on the level of psychological experience are given some form of bodily representation and a partial discharge through anatomical and physiological disturbances. Somatization may be purely sensory, purely motor, purely secretory, or a combination of all. It will be seen that somatizations will fall into four major groups, depending partly upon the structures involved and their psychological and physiological functions, and partly upon the particular aspect of the organ system which is involved. Before discussing these, however, it is necessary to consider the steps by which tensions generated on the psychological level can be translated into somatic dysfunction. These steps constitute a continuous physiological series of increasing complexity, in which the disturbed physiological process becomes dissociated more and more completely both from its original physiological function, and from any conscious ideational content.

All psychosomatic phenomena are produced by the play of opposing forces: human needs and impulses struggling either against external obstacles or dangers, or against internal inhibiting mechanisms such as guilt and anxiety. With any obstruction to the free flow of an impulse towards its gratification the level of internal tension rises. At some point this rising pressure of central excitation must overflow. The overflow may be effectively channeled through some external action with increased energy which overcomes the obstacle and achieves the goal, or it may be diffuse and chaotic; or it may focus on some part function,

setting up what the engineers characterize as a "feed back" system, in which part of the energy output is itself used to reactivate the system.* This state of physiological struggle with mounting tension and discharge is accompanied on the psychological level by frustration, resentment, guilt, and anxiety, with subsequent repression and varying degrees of symbolic representation of the conflict.

The essence of the process consists then in this rising tide of excitation, the functional overflow and the feed-back from this overflow which prevents a total physiological discharge of the energy system unless the functional overflow is effectively channeled. This overflow can be seen to occur in certain definite steps. The rising tide of excitation which is the origin of the entire psychosomatic process, may itself have many sources, all of which have in common the fact that they create tension. Of these, the simplest is the experience of pain; and in outlining these steps pain can be used as the paradigm of all:

Step 1: Pain in an uncomplicated situation gives rise to an automatic reaction of withdrawal or riddance. If this is effective, nothing more happens.

Step 2: Pain is not always mastered so easily. Its source may be internal, or its external source may pursue the victim. This leads to intensified action, such as sustained flight or fight, which calls into action the autonomic functions of the body to reënforce and support the simpler sensori-motor reactions, and to maintain homoeostasis. It is at this point also that the first experience of conscious emotion enters the picture. For this reason it is usually assumed that the autonomic functions are an intrinsic part of the emotional reaction per se. In fact, the entire James-Lange theory was built upon that assumption. Actually the primary relation of the autonomic functions is to the intensified action, and only secondarily to the emotional state.

Step 3: For many reasons, however, pain may not always lead to direct action either of flight or fight. Because of inner conflicts all overt responses may be withheld: and in this situation the individual may feel highly emotional and may have strong autonomic discharges, but without going into action. In fact, in social situations this is one of the frequent human experiences. Everyone is familiar with the occurrence under emotional stress of such phenomena as blushing, sweating, lacrimation, puffing, panting, shivering, shaking, dyspnea, palpitation, polyuria,

* We are indebted for this illuminating suggestion to Dr. Warren S. McCulloch.

and the like. Indeed, so constant is their association with conscious emotions, that they are looked upon as an intrinsic part of the emotional pattern itself. Yet the primary physiological function of each of these phenomena is to assist the body to adjust to changing states of total activity. Emotion comes into the picture only when these efforts encounter obstacles which threaten frustration. However, since some measure of frustration is implicit in almost all human activity, by direct conditioning all such bodily changes, although originally they were related only to alterations in the level of total activity, become secondarily linked to the accompanying emotion. Thus it becomes possible to sweat or blush or puff or palpitate in a moment of emotional excitement, quite apart from any alteration in total activity. For that moment, these phenomena have lost their original physiological functions, and may even have become destructive.

To recapitulate: the physiological phenomena which are ordinarily accepted as inevitable concomitants of emotion per se, were originally the concomitants only of changes in activity. By conditioning they become linked to emotional states, with the result that the emotion, even without any change in total activity, can become the conditioned signal for the physiological change. This constitutes the first step in the sequence of events which we call the psychosomatic process.

Step 4: Guilt and anxiety may lead to a further step in the process of dissociation and repression. "Pain" may be followed by an autonomic discharge alone, with a suppression of all external response and the repression of all conscious emotion. The autonomic physiological phenomena of reënforcement and homoeostasis then occur in the absence of any conscious emotional state at all, or else in a setting of what seem to be "weak" or inadequate emotions. This will be recognized as a clinical syndrome which is as familiar as the common cold, i.e., the individual who has to urinate more frequently than is physiologically indicated, or who sweats or gasps or blushes or pants or palpitates without being aware that his emotions have been stirred. Under these circumstances the physiological processes are often called "emotional equivalents," or else it is said that the emotions were "too weak" to explain the physiological disturbance. Both of these phrases are misleading insofar as they tend to perpetuate the idea that the physiological changes have their origins in the emotional state as such. In all such cases it is easy for the physician to recognize the play of emotion below the surface, even if the patient

TABLE I

| STIMULUS | | PRIMARY REACTION | SECONDARY REACTIONS | PSYCHOLOGICAL REACTION |
|--|----|---|--|------------------------------------|
| <i>Tension-creating stimuli:</i> | | <i>Tension Reducing</i> | <i>Autonomic reënforcement and support and homoeostatic compensatory changes</i> | <i>Conscious emotional arousal</i> |
| Either External— e.g., pain | 1. | Successful effortless withdrawal or "riddance" | 0 | 0 |
| Or Internal— e.g., instinctual demands represented by enteroceptive sensations | 2. | Effortful struggle (fight or flight) | + | + |
| | 3. | 0 (Suppressed) | + | + |
| | 4. | 0 | + | 0 (Suppressed) |
| | 5. | 0 | 0 | 0 |
| | | Overflow to and feed-back from substitutive organ changes | | |

himself succeeds in being unaware of it. These are the everyday, run-of-the-mill anxiety states expressed through mild somatic phenomena. Again, however, it is important not to allow the fact that these are familiar to blind us to their significance as a step in the dissociation of the physiological process from its original function and towards the production of a psychosomatic distortion.

Step 5: The next step is perhaps the most important. All three of the initial components of response are eliminated, i.e., external action, the supporting and reënforcing autonomic functions and the conscious experience of emotion. With the suppression of all of these three immediate reactions, a temporal dissociation occurs. The internal tensions no longer are transitory and episodic, but constant and continuous in their influence on body functions. The discharge of these chronic tension-states then falls logically, physiologically, and psychologically into one of four over-all categories. The discharge may be primarily on the exter-

nal orientative functions, or it may be internalized, or it may focus on the instinctual organs, or it may be diffused. These four alternatives are what lead to the four basic categories of psychosomatic dysfunction.

These steps are represented in Table I.

C. SOMATIZATION

The Four Major Categories:

1. *Organs of External Relationship:* Certain somatizations involve the exteroceptive sense organs, the striated muscles, the organs of speech and their central control, and the central organizing functions of the brain—in short, the organs which subserve the external relationships of the individual, his orientation in space and perhaps in time, his ability to communicate with others, the sensory impressions which reach him from the outside world and his ability to organize them, and his conscious orientative faculties. These are essentially the organs of the Ego, as the term is used psychoanalytically. In current psychiatric parlance, disorders in these functions are ordinarily classified as conversion hysterias. All of these organs occupy a clearly defined place in conscious thoughts. They are the objects of complex ideational processes, which in turn the organs themselves can symbolize.

Yet these organs of external orientation are also served by smooth muscle, blood vessels, and local secretory glands. The motor components of these subsidiary structures are not under conscious voluntary control; and their sensory components are enteroceptors. Examples are the smooth muscle of the eye and of the blood vessels, the sweat glands, pilomotor apparatus and smooth muscle of the skin, the mucous cells of the mucous membranes, and the organs of kinaesthetic sensation, of equilibrium, and of deep pressure and pain. Thus it is only the more external aspects of the Organs of External Relationships that enter fully into our conscious perceptual and ideational world. These subsidiary components have varying degrees of conscious representation; and play a relatively obscure role in the psychic processes which underly and accompany psychosomatic disturbances in this area. They may or may not be involved along with the structures which they serve. Where they are, they mark a transition both physiologically and psychologically between the external somatizations and the deeper somatizations which will be discussed next.

2. *Organs of Internal Economy:* The process of somatization may involve only those internal organs which lie within the interior of the body, and which consequently are hidden from the patient's eyes and largely from his direct knowledge. About certain of these organs everyone has some subjective information, as for instance, the intestinal tract, the bladder, the heart, and the respiratory apparatus. They are known through their excretory products, or from the specific sensations to which they give rise or both. Nevertheless, knowledge of these organs and of their functions is far less precise than is the knowledge of any more external aspect of the body.

Other internal organs such as the bone marrow, spleen, lymph, or blood vessels, give rise to no excreta, and normally to no specific or localized sensory impressions. Under pathological conditions some of them enter consciousness through vaguely localized and non-specific sensations of pressure, distension and pain. Others have no such local signs under any circumstances. Thus they constitute an area of potential body-change which goes beyond the range of subjective experience. Nevertheless, their functions are not free from interaction with psychological levels of experience. The tensions which derive from frustration and from conflicts between opposing inner drives may overflow in such a way as to involve these ghost-like inner functions.

In general, therefore, this large group of internal somatizations includes disorders of the heart and blood vessels, of the respiratory organs, of the gastrointestinal tract, of the liver, pancreas, thyroid, and other endocrine glands.

Clinically, physiologically, psychologically, and from the point of view of psychiatric prognosis, this group presents problems which are distinct from the first. In the first place, just because the interior of the body is mysteriously hidden, and because of the vagueness of the sensations which they generate, disturbances in these functions often give rise to extensive and fantastic psychological elaborations. For this and other reasons, certain of them are often found in a psychotic or pre-psychotic setting. Furthermore, because of the specific importance of the organs involved, and because of the interaction with glands of internal secretion, any interference in their proper functioning has far-reaching and sometimes disastrous secondary effects on the body as a whole, whereas even the most serious disturbance of function in the Organs of External Relationship leaves the body as a whole unimpaired.

3. *Organs of Instinctual Function*: This third group involves the apertures of the body, the organs of intake and output for food, air, and excreta, the swallowing mechanisms of the mouth and throat, the appetites, and all genital functions. Because all of these serve instinctual needs and discharges directly, they constitute foci of special significance. They involve external relationships, but on an elemental instinctual level. They also involve the internal vegetative functions of the body, but only secondarily. Thus they are transitional physiologically as well as anatomically between the organs of External Relationship and of Internal Economy. As examples of disturbances in this group we might mention the dyspareunias, vaginismus, frigidity, all disturbances in male potency, spermatorrhea, air hunger, over-ventilation, sphincter disturbances, retention, constipation, anorexia nervosa, etc.

In current psychiatric thinking, disorders focused on this group are usually linked with one of the other two. Both for theoretical and clinical reasons, however, it is helpful to recognize their special and intermediate significance.

4. *The Body as a Whole*: Finally, there are patients in whom the physiological disturbances or feelings of disability focus on no special organs or areas of the body, but seem rather to involve the entire body, as though it constituted one vague and mystical unit. Here we find states of fatigue and general weakness, of diffuse hypochondriasis, or chronic invalidism, and of fretful neurasthenia. It may fairly be questioned whether these conditions need a separate category of their own. In many instances a careful anamnesis or a period of analytical study makes it clear that diffuse complaints about the body as a whole mask earlier specific disabilities which fall within one of the first three groups mentioned above. In many of the fretful neurasthenias the early and formative stages of the illness are characterized by specific difficulties in one of the instinctual spheres: hence the so-called "sexual neurasthenias." A large proportion of the chronic invalids give an early history of disturbances in the Organs of External Relationship. Many of the diffuse hypochondriases have had earlier difficulties in Organs of Internal Economy.

Nevertheless, in a number of patients diffuse complaints persist that cannot be broken down into earlier disturbances referable to one of the three more localized areas. For this number, however small, it would seem wise to preserve this fourth category, with its diffuse reference to

the body as a whole. Furthermore, this fourth group may have important clinical correlations; and the dynamics of the tendency towards a diffuse body reference may prove to be significantly different from the dynamics of the tendency toward special zones of reference. This clinical group must be more carefully investigated before its relationship to the other three can be settled definitively.

5. *Nomenclature*: We propose, therefore, the following basic groups: Somatizations of the Organs of External Relationship; Somatizations of the Organs of Internal Economy; Somatizations of the Instinctual Organs; and Diffuse Somatizations of the Body as a Whole. Not infrequently, somatizations will occur in more than one body area at the same time; and occasionally different somatizations will alternate with each other. Usually, however, the four basic groups occur independently of each other. It is this, among other considerations, which gives them significance. These terms have the further advantage of being descriptive. They should serve well, therefore, as guides to clinically important and reasonably distinct groupings of psychosomatic phenomena.

A shorter nomenclature for these four basic groups presents certain difficulties. The simplest would be to call them respectively external, internal, instinctual, and diffuse somatizations. The latter three are possibly acceptable. The word "external," however, hardly does justice to the underlying concept. If the word "Ego" were widely used in its analytic connotation and not with its ordinary idiomatic meanings, we might speak of "Ego-organ somatizations." In the absence of any general understanding of this term, however, it would not be useful. It is strange that language has no single word to cover the totality of this function: namely, the orientation of the individual towards the world, his ability to communicate with it, his sensory intake from it, his motor output towards it, and his perceptual organization of this material. This is the function a disturbance in which is usually called an "hysterical conversion," and for which we suggest here the somewhat cumbersome term, "Somatization of the Organs of External Relationship."

Although most psychosomatic disorders fit easily into one of these four categories, dilemmas arise in a few cases. For instance, allergies are usually grouped together because of the presumptive similarity of the underlying biochemical process. Both psychologically and physiologically, on the other hand, the diversified distribution of allergic phenomena is of more importance than its biochemical unity. This makes

it appropriate to place differently situated allergic manifestations in different categories. Similarly, since the skin constitutes a single anatomical structure one might expect to classify all psychosomatic skin disorders together. This would be misleading, however, because psychologically, and to some extent physiologically, the skin subdivides into three functional areas. The exposed areas of the skin of the face and hands constitute an important component of the Organs of External Relationship. The skin around instinctual organs partakes of their physiological and psychological significance. The rest of the skin surface, which is ordinarily covered by clothing, is treated psychologically as though it were an Internal Organ. Obviously these differences must be taken into account in the grouping of skin disorders.

The point of view which has been set forth here is expressed diagrammatically in Figure 1.

6. Discussion of Classification: The major usefulness of such a system of classification as this is to indicate the final common pathway of the psychosomatic process, rather than its secondary physiological supporting mechanisms, or the ultimate sources of the psychological tensions and instinctual energies which converge upon it. It is like naming a wind by the direction towards which it blows rather than that from which it comes.

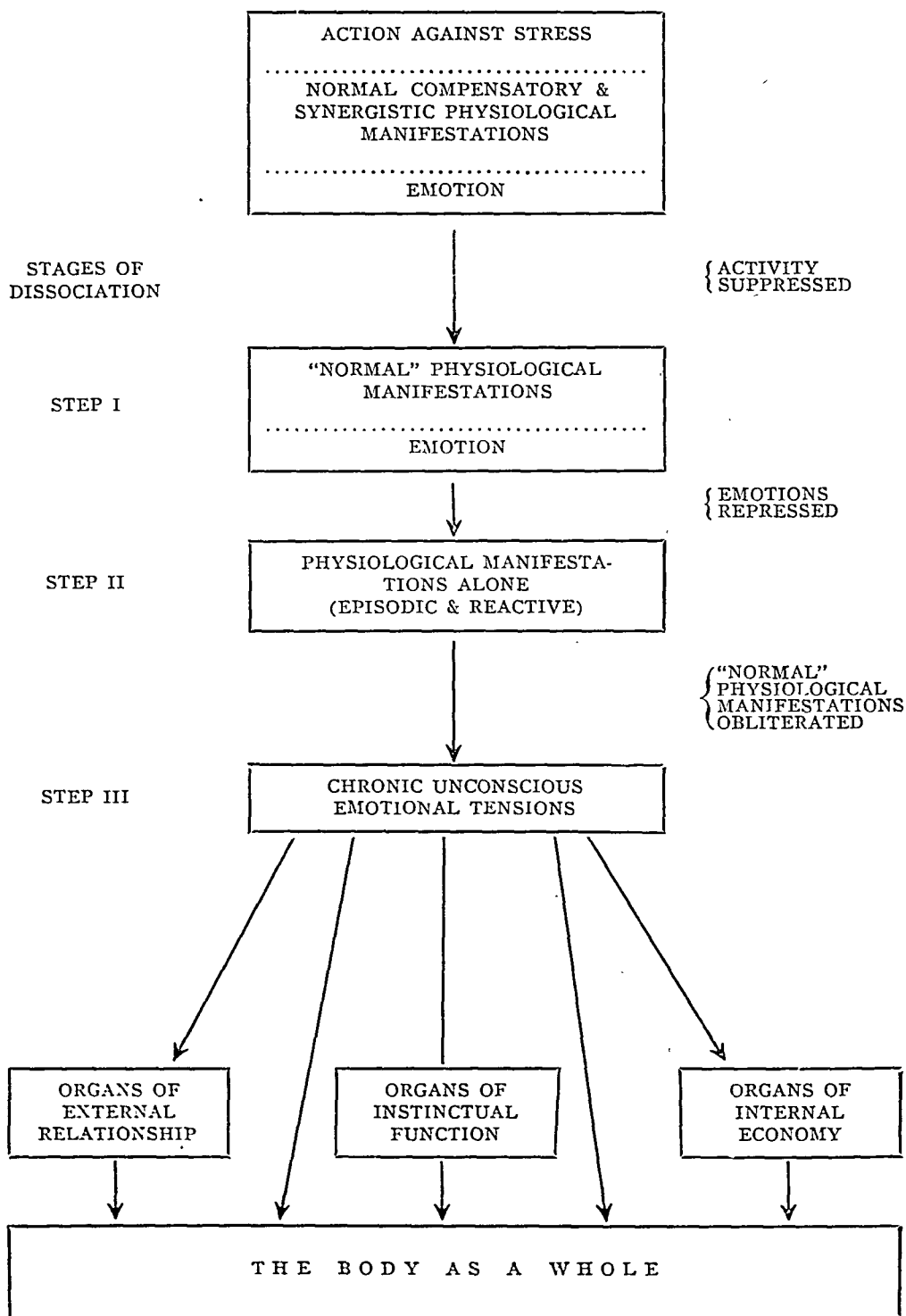
A. Overlapping Areas:

The fact that the process of somatization is rarely if ever focused exclusively on one area without some accessory involvement of the others does not lessen the usefulness of this classification. For instance, in a writer's cramp or an hysterical paralysis of a limb, there may be secondary vasomotor and secretory changes involving vascular structures, the involuntary nervous system, and even such glands of internal secretion as the adrenals. Notwithstanding this, since in such a case it is evident that these play a supportive rather than a primary role, there would be no uncertainty as to its position in this classification, nor is this altered by the fact that any such disturbance in the function of the hands will derive some of its energy from conflicts in the instinctual spheres.

Similarly, a case of Raynaud's disease manifested in the engagement-ring finger after the breaking of an engagement, would be an example of an Internal Somatization; because the primary process is in the autonomic and endocrine control of the vascular tree; and is only secon-

FIGURE 1

THE PROCESS OF SOMATIZATION



daily focused on an organ of external relationship of special emotional significance.

A more complicated problem is presented by the case of a man whose nose would blanch every time he had an erection. The nose is an organ in its own right in terms of respiratory function. Its position on the face makes it at the same time a presenting feature of the personality and thus a component of one of the Organs of External Relationship. Finally, it is involved through the sense of smell in esthetic responses, in eating functions, and in sexual reactions, and in addition is frequently used as a symbolic representative of the genitals. Despite this multiple significance of the nose, since there was no disturbance of instinctual or internal functions, this would be an instance of a somatization of an Organ of External Relationship.

Such a multiplicity of psychological and functional relationships is somewhat rare, but must be taken into account in evaluating the role which any organ or area plays in a psychosomatic disturbance. In the case in point, in which vasomotor change in the nose and in the genital always occur synchronously, a single physiological expression is provided for the multiple underlying conflicts which arise out of instinctual pressures. At the same time it brings into clear relief the significance of instinctual conflicts in external relationships. The expression of most instinctual needs, and particularly of the sexual needs, always involves interpersonal relationships.*

It is not surprising, therefore, that psychosomatic disturbances of sexual functions tend so often to be accompanied by disturbances in the organs of external relationship, or that the latter may be substituted for the former. This was recognized first by Freud as typical for the process which he called the "hysterical conversion" syndrome. Because of the great importance of this observation, a tendency arose to conclude that this association is invariable, and to overlook the fact that disturbances in any organs of instinctual function can occur without involving the organs of external relationship, as for instance in Spermatorrhea. A failure to realize this has led to debates over whether to call Spermatorrhea an "Organ Neurosis" or an "Hysterical Conversion." To call it an Instinctual Somatization is clearly more accurate than either.

* The biological significance of these basic groups was recognized by the late Raymond Pearl⁶ in his lecture on "Constitution and Health." In discussing the relation of the classification of disease to the "innate biological (constitutional) worth or value of certain organ systems," (p. 29), he brings out the fact that certain organ systems come into direct contact with the external environment, whereas others do not; and that profoundly different physiological and psychological consequences derive from this fact.

Disturbances which involve primarily the organs of internal economy occasionally but less frequently have concomitant secondary involvement of other basic areas. At times one area will even alternate with another, e.g., an ulcerative colitis with a dermatitis. All of these overlapping interrelationships make it evident that the four basic areas constitute four points in a series of continuous and not discontinuous phenomena.

B. Ideational and Perceptual Content:

Similarly, with respect to the role that conscious ideational and perceptual processes play in the process of somatization, these four zones highlight four major points in a continuous series. At one end stand the somatizations which involve the most exterior aspects of the organs of external relationship, about which we can perceive and think most clearly. Under stress, however, as was pointed out above, their activities are supported by synergistic functions which bring into play progressively deeper and more obscure internal organs. These range from local sweat glands, and local blood vessels, to the homoeostatic systems which do not enter into conscious ideational processes at all. At the other extreme are the Organs of Internal Economy. The instinctual organs occupy an intermediate place in perceptual and ideational processes, more diffuse in their sensory qualities (i. e., "protopathic"), with a greater degree of reflex automaticity, and functioning with a high degree of automatic coördination with subsidiary vegetative processes.

These considerations lead us to reject any absolute distinction between the disturbances in organs of which we have subjective awareness, and those from which we receive no conscious sensations.

C. Motor versus Sensory:

We would also reject any hard and fast distinction between subjective (sensory) and objective (motor) disturbances. These are differences of degree and not of kind. Recent experiments indicate that there are afferent impulses from and some degree of cortical representation of all viscera. It is only the precise degree, locus, and nature of this representation which remains a matter for further experimental demonstration. If this be true, then a functional overflow from psychological to visceral levels can occur centrally, irrespective of the degree of con-

scious subjective awareness, on the familiar patterns of the conditioned reflex. The specificity of the conscious or unconscious fantasies which are mediated by this central neuronal activity would depend only upon the degree of differentiated, spacially localized sensory modalities by which any particular organ or function is represented. Obviously the exterior aspects of the body are centrally represented with sharper differentiation and greater detail and precision than are the more obscure internal organs. But since these also have central representations, even if to a less sharply differentiated or localized degree, they too are susceptible of involvement in chains of conditioned reflexes and are therefore subject to the same type of overflow as that which mediates the familiar phenomena of the "anxiety equivalent," or the "hysterical conversion syndrome."

Therefore, afferent impulses from all motor activities and from all organ functions must influence the flow of conscious and unconscious fantasy even when these afferent impulses are devoid of specific conscious representation. Similarly all conscious sensory manifestations contain the potentiality of overflow into channels which will disturb organs which themselves have no role in our conscious processes. Thus these differences are superficial and rest upon no basic differences of mechanism. The intimate interweaving of all afferent and efferent phenomena in the functioning of the central nervous system makes unwarranted any classificatory differentiations on the basis of sensory or motor, conscious or unconscious.

III. THE PSYCHOPATHOLOGICAL SETTING

The clinical evaluation of such illnesses depends partly upon the type of somatization, and partly on the general psychopathological setting in which it occurs. For the evaluation of the whole picture, therefore, the psychopathological settings may be divided into four major categories.

- a. The psychoneurotic constellations
- b. Neurotic behavior disorders
- c. Psychopathic behavior disorders
- d. The psychoses

The *addictions and perversions* constitute a fifth aspect of the psychopathological setting, whose relationships to psychosomatic disorders must also be considered. It is not necessary here to present in full the

FIGURE 2
PSYCHOSOMATIC INTERRELATIONSHIPS

| <i>Organic</i> | <i>Psychological</i> |
|---|---|
| <i>Susceptibility</i> (to trauma, infections, circulatory disturbances, biochemical disturbances and deficits, new growths, etc., etc.) | <i>Psychophysical Types</i> |
| | { Physiological Morphological Psychological |
| <i>Somatizations</i> | <i>Psychopathological Settings</i> |
| Organs of External Relationships | Psychoneuroses |
| Organs of Internal Economy | Neurotic Behavior Disorders |
| Instinctual Organs | Psychopathic Behavior Disorders |
| Body as a Whole | Psychoses |

argument for the grouping of the psychoneuroses together into a general category of psychoneurotic constellations, nor for the differentiation between neurotic behavior disorders and psychopathic behavior disorders. Out of these relationships, however, the above general diagnostic diagram may be evolved (Figure 2).

From this diagram it should be evident that in the characterization of psychosomatic disorders, a simple terminology can hardly be adequately descriptive. Thus, a case of psychogenic impotence can be adequately characterized only by some descriptive term which will indicate also the nature of the psychopathological setting such as "an instinctual somatization in a psychosis," or in a psychopathic behavior disorder, or in a neurotic behavior disorder, a neurosis, a neurotic depression, or an anxiety neurosis. Or, when as sometimes happens, the somatic disturbance tends to alternate with some other form of psychopathology, this must be indicated by inserting the words "alternating with" between the two components of the descriptive label, e.g., "instinctual somatization *alternating with* neurotic depression." These phrases are offered merely as examples of the terminology which would grow out of this approach.

IV. CODIFICATION

An increasing number of hospitals are studying the psychosomatic

relationships of the processes of disease. Inquiries addressed to these hospitals have revealed considerable perplexity over the problem of codifying, indexing, and filing clinical data in such a way as to make the many details easily and rapidly available for research purposes.

A tentative plan of codification is therefore suggested here, growing out of the classification we have described, in order to instigate a study of the problem by those who are experienced in the relation of the classification and codification of disease to statistical analyses.

1. *Suggested Addition to the Standard Classified Nomenclature of Disease:* In the system of numerical codification of the Standard Classified Nomenclature of Disease, the topographical site of the disease process is indicated by numbers which precede the dash, and the nature of the etiological agent by numbers which follow it. Because the site of the disease has psychosomatic importance, both physiologically and psychologically, and also because any new system of codification should make use of existing systems, it is suggested that the same general order should be followed for the codification of psychosomatic phenomena.

Certain additions are necessary, however, in order to include psychosomatic considerations in the standard codification of disease. The psychosomatic process involves the personality as a whole, mediating its influence through the nervous system and manifesting itself either in the body or in some part of it. Although a specific area or organ may be the site of the disturbance, the disease process arises in the whole personality and not in any one organ, not even in the nervous system. Therefore, if we limited ourselves to topographical categories alone, we would indicate not the site of the disease process but merely the part of the body which is being used to express a disorder of the whole psychobiological unit. Therefore, and because of the multidimensional nature of psychosomatic considerations, we end up with an index number which may consist of as many as five units.

a. It would seem wise to introduce the psychosomatic constellation as a new sub-unit under OO "Psychobiological unit." This new unit might be called the "psychosomatic unit," and it could then be codified as follows:

- OOI —Somatizations of organs of External Relationship
- OOII —Somatizations of Organs of Internal Economy
- OOIII—Somatizations of Instinctual Organs
- OOIV—Somatizations of the Body as a Whole

b. An additional topographical indication is then needed, as in the existing code, to identify the precise organ of the body involved. This could be provided by introducing after the dash, the code numbers appropriate to the area or organ which is the site of the chief disturbing somatic symptoms.

c. As in the existing code the etiological categories would follow, but present certain difficulties. In the Standard Classified Nomenclature the accepted categories of causes are: prenatal influence (category "O"), infection (categories 1 and 2), intoxication (category 3), trauma (category 4), anemia, ischemia, thrombosis, and other such circulatory disturbances (category 5). Diseases which are secondary to "disturbances of innervation or of psychic control" fall into categories 5.5 to 5.9. Mechanical obstructions or abnormalities fall into category 6; disorders of metabolism, growth and nutrition, category 7; new growths, category 8; unknown disease processes, degenerative, inflammatory, hereditary, and familial, etc., categories 9 and 10; undiagnosed disease, category Y. It is evident that among existing categories the one which will be applicable to our problem most frequently is category 5.5, "diseases secondary to disturbances of innervation and psychic control," which includes code numbers for almost all possible motor and sensory disturbances, disturbances of sympathetic and parasympathetic innervations, and reflex disturbances. However, the psychosomatic interrelationships are significant in many other etiological processes (glandular, chemical, infectious, etc.) and their appropriate codification makes it necessary to provide a place for the inclusion of this whole section of the standard classification.

In order to introduce as little change as possible, the etiological classification could therefore be introduced after the second dash.

d. This would have to be followed by the code number for a psychopathological setting. Thus an hysterical flaccid paralysis of the upper extremity would be codified as follows: 001-080-560.

e. The final unit in the full code would indicate the presence of additions or perversions.

2. *Standard Psychiatric Classification Approved by the American Psychiatric Association:* In the special section on the classification of mental disorders which has been approved by the Council of the American Psychiatric Association, the psychosomatic disorders would have

FIGURE 3

| CASE SUMMARY | | | | CODIFICATION | | |
|--|-----|---------|---------|--|---|------------------------------|
| Name | Age | Hosp. # | Service | Standard Classified Nomencl. of Disease | Approved Psychiatric Classification—A.P.A. | |
| | | | | | Standard | Condensed |
| Medical and/or Surgical diagnosis | | | | q. v. | | |
| Socio-familial Diagnosis — (Economic and social level, position in family —marital status—occupation) | | | | | | |
| Conventional Psychiatric Diagnosis (if any) | | | | | q. v. | q. v. |
| PSYCHOSOMATIC SUMMARY | | | | | | |
| A. Somatizations of the Organs of External Relationships Organs of Internal Economy Instinctual Organs Body as a Whole | | | | | 00I 00II 00III 00IV | 25I 25II 25III 25IV |
| B. Organ or Body Area Involvement (Standard Classified Nomenclature—Topographical) | | | | q. v. | | |
| C. Etiological and Pathophysiological Classif. (Standard Classified Nomencl.—Etiological) | | | | q. v. | | |
| *D. Psychopathological Setting | | | | | | |
| General | | Special | | | | |
| 1. Psychoneurosis | | | | | 002-x00 to 002-x33 & x0x | 161-167 |
| 2. Neurotic Behavior Dis- order | | | | | 000-x61 000-x71-3 | 241-242 |
| 3. Psychopath. “ “ | | | | | 000-x40 | 2361-2364 |
| 4. Psychosis | | | | | q. v. | q. v. |
| *E. Addictions and/or Perversions | | | | | 000-332 000-3xx 000-x41 | 232-233 2361 |
| Cumulative Codification | | | | | (Order: A, B, C, D, E) | |

* These code numbers are from the approved psychiatric nomenclature. They are wholly unsatisfactory; but must be used until the basic classification is improved.

to be introduced as an additional category, OOI to OOIV, with the subdivisions already indicated:

OOI —Somatizations of Organs of External Relationship

OOII —Somatizations of Organs of Internal Economy

OOIII—Somatizations of Instinctual Organs

OOIV—Somatizations of the Body as a Whole

Neurasthenia and hypochondriasis would be transferred from their present position in the code to the Somatizations of the Body as a Whole. The "conversion hysterias" would be transferred to the Somatizations of Organs of External Relationship; and code numbers would be provided for the Somatizations of Organs of Internal Economy and Somatizations of Instinctual Organs, whose very existence is not recognized in the existing standard nomenclature.

3. *Condensed Form:* In the official condensed form of the new classification adopted by the Committee on Statistics and approved by the Council of the American Psychiatric Association, the psychosomatic disorders could be added to the existing list as follows:

25 *Psychosomatic Disorders:*

25I —Somatizations of Organs of External Relationship

25II —Somatizations of Organs of Internal Economy

25III—Somatizations of Instinctual Organs

25IV—Somatizations of the Body as a Whole

As in the more complete code, the hysterias, the hypochondriacal and the neurasthenic states will have to be transferred to their appropriate setting under this new classification.

Furthermore, the general psychopathological setting in which the psychosomatic disturbance occurs can be indicated readily by the appropriate code number after the dash. For instance, a Somatization of Organs of External Relationship in a psychoneurotic setting would be codified as 25I-16; in a neurotic behavior disorder as 25I-24; in a psychopathic personality as 25I-236; and in a setting of psychosis as 25I- followed by the number appropriate to the particular type of psychotic disturbance which is found to be present.

A face-sheet for summarizing psychosomatic records is appended.

SUMMARY

Psychosomatic interrelationships indicate the processes by which energies which are generated on the psychological level of experience

can be translated into disturbances of somatic functions. The process of somatization is viewed as a series of successive stages in the dissociation of a physiological process from its original physiological purpose. The following steps are recognized: (1) Normal compensatory and synergistic physiological mechanisms are brought into play in order to reënforce action against internal or external obstacles. (2) Because this usually occurs in a setting of a consciously perceived emotion, a conditioned link is established between the emotion and these some bodily mechanisms of reënforcement and overflow, even without stressful action. (3) The physiological manifestations of reënforcement and overflow can occur alone, without either stressful action or conscious emotion. (4) The sustained influence of chronic unconscious inner tension can then overflow into one of four channels, involving: (a) Organs of External Relationship, (b) Organs of Internal Economy, (c) Instinctual Organs, (d) Diffuse Involvement of the Body as a Whole.

The clinical evaluation of any of these states of somatization depends (a) upon the type of somatization, and (b) upon the psychopathological setting in which it arises. This gives rise to a descriptive nomenclature which has clinical and prognostic implications, and (c) to a possible system of codification which can be constructed on the foundations of the Standard Classified Nomenclature of Disease.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

OCTOBER 7—*The New York Academy of Medicine*. ¶Executive session. Reading of the minutes. ¶Papers of the evening. Status of penicillin, clinical viewpoint. Chester S. Keefer, Wade Professor of Medicine; Boston University School of Medicine.

OCTOBER 28—*The Harvey Society in affiliation with The New York Academy of Medicine*. The First Harvey Lecture, "Some Observations on Pain," Harold G. Wolff, Associate Professor of Medicine, Cornell University Medical College. This lecture takes the place of the Second Stated Meeting of the Academy for October.

NOVEMBER 4—*The New York Academy of Medicine*. Executive session—a] Reading of the minutes; b] Report of Nominating Committee. ¶Papers of the evening. ¶Present Status of the Treatment of Pneumonias—a] Treatment of lobar pneumonia, Norman Plummer, Major, M.C., A.U.S., Cornell University Medical College; b] The use of penicillin in the treatment of lobar pneumonia and pneumococcal empyema, William S. Tillett, Professor of Medicine, New York University College of Medicine. ¶Report on election of Fellows.

NOVEMBER 18—*The Harvey Society in affiliation with The New York Academy of Medicine*. The Second Harvey Lecture, "Recent Work on the Respiratory Chemistry of the Blood," F. J. W. Roughton, F.R.S., Fellow of Trinity College, Lecturer in Physiology, Cambridge University.

This lecture takes the place of the Second Stated Meeting of the Academy for November.

SECTION MEETINGS

OCTOBER 1—*Section of Surgery*. ¶Reading of the minutes. ¶Papers of the evening—a] The importance of missile velocity in the production of wounds, George R. Callender, Col., M.C., USA Director of Army Medical School, Washington, D. C. (by invitation); b] Battle casualties as seen at the Halloran General Hospital, George K. Carpenter, Maj., M.C., AUS (by invitation); c] Blast injuries in naval warfare, Rupert H. Draeger, Comdr. (M.C.), USN, Naval Medical Research Institute, Bethesda, Maryland (by invitation). ¶General discussion. ¶Executive session.

The following Sections canceled their regular meetings October 11 to 22 in favor of the Graduate Fortnight: Neurology & Psychiatry, Pediatrics, Ophthalmology, Genito-Urinary Surgery, Orthopedic Surgery, Medicine, Otolaryngology.

OCTOBER 26—*Section of Obstetrics and Gynecology*. Executive session. ¶Reading of minutes. ¶Case reports.—a] Efficacy of penicillin after failure of sulfa drugs in bloodstream infection following vaginal plastic operation. Alfred M. Hellman, E. Fluth Guilfoil (by invitation) b] Artificial insemination aided by vaginal diaphragm, Boris A. Kornblith. ¶Papers of the evening—a] The mechanism of transplacental isoimmunization by the Rh factor (Also a brief review of work done to date on the Rh factor), Philip Levine; b] Vulvovaginitis in children, Rose H. Andre (by invitation). ¶General discussion, I. Rubin, Harry Green (by invitation).

NOVEMBER 3—*Section of Dermatology and Syphilology*. Presentation of cases—a] From the Skin and Cancer Unit, New York Post-Graduate Medical School

and Hospital; b] Miscellaneous cases. ¶ General discussion. ¶ Reading of the minutes. ¶ Executive session.

NOVEMBER 5—*Section of Surgery*. Reading of the minutes. ¶ Presentation of cases—a] Cases of spine fracture from the Knickerbocker Hospital, Philip D. Allen; b] Cases of shoulder "cuff" injury from St. Luke's Hospital, Frederick R. Thompson. ¶ Papers of the evening—a] Some new conceptions of the differential diagnosis and treatment of shoulder "cuff" injuries, Harrison L. McLaughlin; b] Essentials in the treatment of fractures and dislocations of the spine, Arthur G. Davis, Erie, Pennsylvania (by invitation). ¶ General discussion. ¶ Executive session.

NOVEMBER 9—*Combined Meeting of the New York Neurological Society and the Section of Neurology and Psychiatry*. ¶ Presidential address. The nature of psychogenic cure, C. P. Oberndorf. ¶ Papers of the evening—a] Integration of the electroencephalogram—An approach to schizophrenia through electroencephalography, Charles S. Roberts, M.A. (by invitation); William J. Turner (by invitation); b] Physiological and clinical aspects of the electroencephalogram, Tracy J. Putnam, Paul F. A. Hoefer. ¶ Discussion—Bernard L. Paccella.

NOVEMBER 10—*Section of Historical and Cultural Medicine*. ¶ Reading of the minutes. ¶ Paper of the evening. The history of aviation medicine, Victor Robinson. ¶ Discussion—Robert John Hunter, Lt. Commander, (MC) USN (Ret.) (by invitation), Louis Hopewell Bauer (by invitation), and Beeckman J. Delatour.

NOVEMBER 11—*Section of Pediatrics*. ¶ Reading of the minutes. ¶ Presentation of cases. ¶ Papers of the evening—a] Vitamin D in human milk, Benjamin F. Kramer, L. Polskin, Ph. D. (by invitation), A. S. Sobel (by invitation). ¶ Discussion—

J. M. Lewis; b] A study of the regulation of the level of vitamin A in the blood of newborn infants, J. M. Lewis, O. Bodansky (by invitation), L. M. Shapiro (by invitation). ¶ Discussion—Samuel Z. Levine; c] Niacin deficiency in children, Harry Bakwin, James Winn (by invitation), Margaret Tenbrinck (by invitation); ¶ Discussion—H. D. Kruse (by invitation). ¶ General Discussion.

NOVEMBER 15—*Ophthalmology*. ¶ Instruction Hour 7:00 o'clock; Fundus lesions, Ralph I. Lloyd. ¶ Reading of the Minutes 8:15 o'clock; ¶ Case Reports—a] Spielmeier-Vogt's disease—a study of its pathology, Isadore Givner, Leon Roizin (by invitation); b] Monocular exophthalmos due to hyperthyroidism in a patient with Duane's syndrome, W. Guernsey Frey; ¶ Papers of the Evening—a] Fundus changes in the various forms of arterial hypertension, Herman Elwyn; ¶ Discussion—Herman O. Mosenthal; b] The ocular fundus in urological disease associated with systemic hypertension, Martin Cohen. ¶ Discussion—Arthur M. Fishberg; c] Ocular pathology in experimental hypertension, Irving Graef, Robert K. Lambert.

NOVEMBER 16—*Medicine and The New York Associated Allergy Clinics*. ¶ Papers of the Evening—a] Management of the asthmatic patient, Will C. Spain, *New York Post-Graduate Hospital*; b] Eczema, Robert A. Cooke, *Roosevelt Hospital*; c] Newer conceptions of hay fever immunization, Mary H. Loveless, *New York Hospital*. ¶ Round Table Discussion—Robert A. Cooke, *Chairman*, Robert Chobot, A. Benson Cannon, Matthew Walzer.

NOVEMBER 17—*Genito-Urinary Surgery*. ¶ Reading of the minutes. ¶ Paper of the Evening—Management of postoperative urinary tract complications, Earl E. Ewert, *Lahey Clinic, Boston* (by invitation). ¶ General Discussion—Clar-

ence G. Bandler, R. B. Henline. ¶ Executive session.

NOVEMBER 17—*Otolaryngology*. ¶ Reading of the Minutes. ¶ Papers of the Evening—
a] Experimental investigation of cigarette smoke and its effects, Arthur W. Proetz, Professor of Clinical Otolaryngology, Washington University School of Medicine, Saint Louis, Missouri (by invitation); b] The use of sulfa drugs in the mastoidectomy wound where complete closure is employed, Arthur J. Herzig; c] 1—Unusual case of osteoma of the nasal accessory sinuses; 2—Moving picture; Radical fronto-ethmoidal operation, James Swift Hanley. ¶ Discussion—Wesley C. Bowers, John D. Kernan, Irving Schwartz.

NOVEMBER 19—*Orthopedic Surgery*. ¶ Reading of the Minutes. ¶ Presentation of Case—*From the New York Orthopedic Dispensary and Hospital*—Osteodystrophia fibrosa associated with pigmentation of skin, Paul J. Strassburger (by invitation). ¶ Papers of the evening—
a] Rehabilitation of war wounded, T. Campbell Thompson, Lt. Colonel, M. C.; b] Practical application of physical therapy in rehabilitation, William Benham Snow (by invitation). ¶ General Discussion—Opened by Kristian G. Hansson. ¶ Executive Session.

NOVEMBER 23—*Obstetrics and Gynecology*. ¶ Executive Session—Reading of the minutes. ¶ Case reports—
a] Efficacy of penicillin after failure of the sulfa drug in case of pregnancy complicated by gonorrhea, Hyman Strauss (by invitation). NOTE: *The main points about this new and apparently spectacular drug, penicillin, will be crystallized and illustrated with slides.* ¶ Paper of the evening—Vulvo-vaginitis in children, Rose H. Andre (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

New York Roentgen Society (in affiliation with *The New York Academy of Medicine*—Because of conflict in dates with the Graduate Fortnight, this Society held no meeting in October.

OCTOBER 28—*The New York Pathological Society* (in affiliation with *The New York Academy of Medicine*). ¶ Presentation of cases—
a] Extragenital chorio-epithelioma: its relation to teratoid vestiges in the testes, Antonio Rottino and Hannibal De Bellis (by invitation); b] Non-suppurative nodular panniculitis, David M. Spain (by invitation) and Joseph M. Foley (by invitation). ¶ Papers of the evening—
a] Myasthenia gravis: discussion of possible underlying mechanism, Herbert C. Stoerk; b] Changes in the testes in hepatic insufficiency, Thomas C. Morrione (by invitation). ¶ Executive session.

NOVEMBER 15—*New York Roentgen Society*. ¶ Papers of the evening—*Program from Roosevelt Hospital*;
a] Pulmonary emphysema, Walter W. Brandes (by invitation); b] Pulmonary infarction, Arthur Antenucci (by invitation); c] The role of the sulphonamides in the treatment of ulcerative colitis, Moore A. Mills (by invitation); d] Some manifestations of gastrointestinal allergy, William H. Boone. ¶ Executive session.

NOVEMBER 18—*The New York Pathological Society*. ¶ Presentation of cases—
a] Sacrococcygeal chordoma with metastases, Lotte Graf (by invitation); b] Cystomyoma of seminal vesicle, arising from Müllerian remnants, Alfred Plaut. ¶ Papers of the evening—
a] Traumatic intracerebral and intrapontine hemorrhage without skull fracture, Alfred Angrist; b] Subdural suppuration originating from purulent leptomeningitis, Eugene D. Spitz (by invitation), Ann Pollak (by invitation). ¶ Executive session.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

- Bailey, H. & Love, R. J. M. *A short practice of surgery*. 6 ed. London, Lewis, 1943, 1033 p.
- Bert, P. *Barometric pressure; researches in experimental physiology*. Columbus, O., College Book Co., 1943, 1055 p.
- Everett, M. R. *Medical biochemistry*. N. Y., Hoeber, [1942], 694 p.
- Friedman, R. *Biology of *Acarus scabiei**. N. Y., Froben, 1942, 183 p.
- Gradwohl, R. B. H. *Clinical laboratory methods and diagnosis*. 3 ed. St. Louis, Mosby, 1943, 2 v.
- Kolmer, J. A. *Clinical diagnosis by laboratory examinations*. N. Y., Appleton-Century, [1943], 1239 p.
- Manheim, S. D. *Proctology*. N. Y., Oxford Univ. Press, [1943], 137 p.
- Ogilvie, R. F. *Pathological histology*. 2 ed. Edinburgh, Livingstone, 1943, 411 p.
- Preston, F. E. *The ophthalmic prescriber's codex*. London, Lewis, 1943, 176 p.
- Samuels, S. S. *Peripheral vascular diseases*. N. Y., Oxford Univ. Press, [1943], 84 p.
- Textbook (A) of medicine by American authors*, edited by R. L. Cecil. 6 ed. Phil., Saunders, 1943, 1566 p.
- Walshe, F. M. R. *Diseases of the nervous system*. 3 ed. Edinburgh, Livingstone, 1943, 350 p.
- Williams, A. E. *Barnardo of Stepney*. London, Allen, [1943], 236 p.
- Wolf, S. G. & Wolff, H. G. *Human gastric function*. N. Y., Oxford Univ. Press, [1943], 195 p.

DEATHS OF FELLOWS

BELL, GEORGE HUSTON: 30 East 40 Street, New York City; born in Mt. Sydney, Virginia, August 10, 1866; died in New York City, October 5, 1943; graduated in medicine from the University of Virginia Department of Medicine in 1897; elected a Fellow of the Academy March 3, 1904.

Dr. Bell was consultant ophthalmic surgeon to the New York Eye and Ear Infirmary; eye consultant to the U. S. Public Health Service, U. S. Marine Hospital No. 70; a diplomate of the American Board of Ophthalmology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the American Ophthalmological Society and the State and County Medical Societies.

BUERGER, LEO: 530 Park Avenue, New York City; born in Vienna, Austria, September 13, 1879; died in New York City, October 6, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1901; elected a Fellow of the Academy February 4, 1909.

Dr. Buerger was formerly professor of surgery (urology) at the College of Medical Evangelists, Loma Linda and Los Angeles; for many years on the staff of Mount Sinai Hospital; attending surgeon to the Beth David and Bronx Hospitals; consultant in the genito-urinary department at Israel Zion Hospital and attending urologist to the Wyckoff Heights Hospital. He was a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Urological Association, the American Association of Pathologists and Bacteriologists and the California Medical Association. He was a contributor to various medical journals; the author of "Circulatory Disturb-

ances of the Extremities"; the discoverer of Buerger's disease; assisted in the development of the Brown-Buerger cystoscope; devised an operating cystoscope, the cystourethroscope, and other urologic instruments.

ELLIS, ZENAS HORACE: 58 East 65 Street, New York City; born in Poultney, Vermont, February 14, 1896; died in New York City, October 20, 1943; graduated in medicine from the University of Vermont in 1920; elected a Fellow of the Academy November 4, 1937. He was a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, a member of the American Academy of Ophthalmology and Otolaryngology, and a member of the State and County Medical Societies.

LOHMAN, WILLIAM HENRY: 431 Washington Avenue, Brooklyn, New York; born in West Orange, New Jersey, May 9, 1881; died in Brooklyn, August 8, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1904; elected a Fellow of the Academy March 3, 1927; and served the Academy as a member of the Committee on Public Health Relations, 1937 through 1939.

Dr. Lohman was professor of clinical medicine at the Long Island College of Medicine; chief attending physician to the Brooklyn Hospital, consulting physician to the North Country Community Hospital, Glen Cove, and St. John's Hospital; a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association and a member of the State and County Medical Societies.

During the World War, Dr. Lohman was chief of the medical service of Navy Base Hospital Number One, Brest, France, and was cited by the Navy Department for his services.

THOMEN, AUGUST STEPHEN ASTOR: 667 Madison Avenue, New York City; born in New York City, January 16, 1892; died in New York City, September 11, 1943; graduated in medicine from University and Belle-

vue Hospital Medical College in 1918; elected a Fellow of the Academy January 6, 1927.

Dr. Thomen was at one time attending physician to the allergy clinic of the New York Hospital, and from 1927 to 1935 director of the allergy clinic of the College of Medicine, New York University. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

VON WEDEL, HASSOW OTTO: Ardsley-on-Hudson, New York; born at Dobbs Ferry, New York, November 18, 1886; died at Ardsley-on-Hudson, October 10, 1943; graduated in medicine from New York University College of Medicine in 1920; elected an Associate Fellow of the Academy April 19, 1928. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

WILE, IRA SOLOMON: 264 West 73 Street, New York City; born in Rochester, New York, November 29, 1877; died in New York City, October 9, 1943; graduated in medicine from the University of Pennsylvania Department of Medicine in 1902; elected a Fellow of the Academy January 9, 1927.

Dr. Wile was associate pediatrician at The Mount Sinai Hospital, a diplomate of the American Board of Psychiatry and Neurology, a member of the Board of Education, 1912-1918, a member and President in 1932 of the American Orthopsychiatric Association, a member of the American Psychiatric Association, the American Public Health Association, the American Speech Correction Association, the National Committee for Mental Hygiene, the International Committee for Mental Hygiene, the Society for the Advancement of Education, the American Child Health Association, the Medical Societies of the State and County, and a Fellow of the American Medical Association. He was the author of numerous books, a contributor to many medical publications and lecturer in educational hygiene at New York University and Columbia University.

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



FEBRUARY 1944

THE TREATMENT OF LOBAR
PNEUMONIA *

NORMAN PLUMMER, Major, M.C., A.U.S.

L LOBAR PNEUMONIA, as it was known a comparatively few years ago,^{1,2,3} no longer exists today. What Bellevue Hospital intern now would believe that ten years ago there were as many as one thousand cases of lobar pneumonia on the adult medical service during a single winter season? Or that during some seasons single wards admitted more than one hundred patients with this disease? Or that at times during the winter more than half of the patients in a large ward had lobar pneumonia? In the winter of 1927-1928 when we were studying serum from three of the four medical services at Bellevue, we included in our series 166 type I pneumonias; 169, type II; 44, type III; and 159 Group IV cases. Would not the investigators of today glory in such a service!

During this period and up to the time of the introduction of sulfa-pyridine, pneumonia was a highly fatal disease. At Bellevue Hospital the gross fatality rate never dropped below 30 per cent, in spite of all our efforts with serum. Type II and type III pneumonia almost always had a mortality rate of over 50 per cent.

* From The New York Hospital and Department of Medicine, Cornell University Medical College, New York, N. Y.
Presented November 4, 1943 before the Stated Meeting of The New York Academy of Medicine.

The gross fatality rate now is less than 10 per cent, and that holds for type II and usually for type III pneumonia as well. The number of cases is greatly reduced. In a period of three years now we would not expect to follow the series of typical lobar pneumonias that formerly could be seen in a single winter. However, the greatest transformation of all is in the length and course of the disease in the individual case. Even in places like Bellevue Hospital, one now rarely sees the very sick pneumonia patient such as described by Osler, ". . . when the picture presented is more distinctive than that presented by any other acute disease. The patient lies often on the affected side; the face is flushed, particularly one or both cheeks; the breathing is hurried, accompanied often with a short expiratory grunt; the alae nasi dilate with each inspiration; herpes is usually present on the lips or nose; the eyes are bright, the pupils are often unequal, the expression is anxious, and there is a frequent short cough which makes the patient wince and hold his side. The expectoration is blood-tinged and extremely tenacious. The temperature may be 104° or 105° . The pulse is full and bounding and the pulse-respiration ratio much disturbed." The later stage, of extreme abdominal distention, severe delirium or terminal circulatory collapse is observed even less frequently. Complications such as pneumococcal arthritis, severe hepatitis, multiple abscesses, and parotitis now are almost never seen.

This change in pneumonia as a disease has come chiefly during the past five years, during which time there have been tremendous advances in its therapy. First came the advance from serum to sulfapyridine, then to sulfathiazole and sulfadiazine, and finally, tonight you will hear from your next speaker about the most recent and perhaps the most remarkable development, the use of penicillin. During the remainder of my presentation I shall outline for you present therapy of pneumonia, particularly the use of the sulfonamides, and shall describe the results to be expected when the measures outlined are employed.

The symptomatic and supportive treatment of pneumonia still should be emphasized, even though it has changed greatly from that formerly required. Attention must be given to the nursing details—a proper arrangement of the sickroom, bathing, fluid and food intake, elimination, sedation—all of which must be individualized. Usual recommendations are: absolute bed rest during the acute period of illness; fluids between 2,000 and 3,000 cc. for the average adult patient; a simple

nutritious diet with consideration of vitamin intake; the judicious use of cathartics and enemas, preventing constipation but at the same time avoiding unnecessary intestinal irritation or moving of the patient; and sedation that is neither overprescribed nor unkindly withheld. Oxygen occasionally has great value but now is desirable in only a small percentage of the cases. Measures for the control of severe abdominal distention such as pituitrin and the rectal tube and turpentine stupes are needed only infrequently. Adrenalin, strychnine, caffeine, camphor, coramine no longer carry the same significance in pneumonia therapy. These procedures, nevertheless, must not be forgotten or neglected, because when they are needed they are needed urgently and promptly. In addition, the value of glucose and saline infusions or hypodermoclyses for the maintenance of the proper water and salt balance, and the use of 50 per cent glucose or sucrose intravenously for pulmonary edema always must be kept in mind.

We shall proceed now from the general to the specific treatment of pneumonia, and first of all discuss the present value of antipneumococcal serum. At the time of the introduction of sulfapyridine in 1938, serum was being used widely in the treatment of pneumococcal pneumonia. While many cases showed spectacular responses, there were many discouraging failures and the gross mortality in large series was not convincingly affected, although in some types a substantial reduction in the mortality rate was achieved. At Bellevue Hospital we had used serum for many years; we strongly favored its use; and after our early experience with sulfapyridine we believed that a combination of serum and sulfonamide would probably be the treatment of choice. We thereupon commenced a statistical study to prove or disprove this point. At the conclusion of an alternate-case study⁴ made over a period of two and a half years, we found no appreciable difference between the effects of sulfonamide alone and those following sulfonamide and serum. The mortality, duration of illness, and incidence of complications were the same in both groups. We concluded that serum had no role except in those patients who could not tolerate or did not respond within 24 to 48 hours to the sulfonamide drugs. At the time, this was a bold conclusion and considerably criticized. But time has borne it out, and today serum has proven of value in only an occasional case.

Pneumonia caused by a sulfonamide-resistant pneumococcus is occasionally encountered. Tillett⁵ has reported two such cases, both of

TABLE I
SULFONAMIDE DRUGS USED IN PNEUMONIA

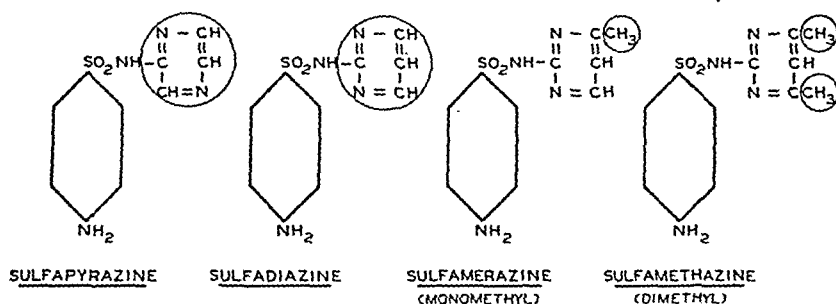
| | |
|---|--|
| Sulfanilamide (Prontylin) | Ineffective. Should <i>not</i> be used. |
| Neoprontosil | |
| Prontosil | |
| Sulfapyridine | Toxic. Should <i>not</i> be used. |
| Sulfadiazine | Most effective and |
| Sulfathiazole | least toxic. |
| Sulfapyrazine | Derivatives of sulfadiazine; |
| Sulfamerazine | still under investigation. |
| Sulfamethazine | |
| Sodium Salts of all the sulfonamides..... | Soluble; used for intravenous and other parenteral therapy. |

which responded promptly to serum after failures with sulfonamides. During the past year at The New York Hospital we discovered a resistant type IV pneumococcus pneumonia which was benefited by serum. These resistant infections are infrequent, but they present a positive indication for serum. In addition, there is the case, even more uncommon than the one with a resistant infection, in which there is a severe sulfonamide intolerance and in which the drug should not be given. Such cases occurred much more commonly with sulfapyridine than with the newer sulfonamides. It is reasonable to suspect that in the future sulfonamide-resistant infections and drug-sensitive individuals will play a much greater role in pneumonia; but I dare say that after hearing Tillett's report, you will agree that when penicillin becomes generally available this drug and not serum will furnish the answer to this problem.

The sulfonamide drugs which have been used for pneumonia now form a very imposing list, but it can be divided readily into sulfonamides that should not be used in pneumonia, those that are most effective, and those that remain under investigation. It is most important, I believe, to emphasize that some of the drugs are comparatively ineffective or too toxic for further use.

Sulfanilamide, and prontosil and neoprontosil (which break down in the body to sulfanilamide) were the first sulfonamides to receive trial in pneumonia. However they were toxic and almost without clinical

STRUCTURAL FORMULAE OF SULFADIAZINE
AND THREE OTHER CLOSELY RELATED SULFONAMIDE DRUGS



effect in this disease, and today they have no place at all in its treatment. Next came sulfapyridine, which was effective but probably one of the most disagreeable drugs that man has ever had prescribed for him. Its taste was bland and chalky, but in almost every case it produced severe nausea and apathy, and persistent vomiting in more than half. This was in addition to a relatively high incidence of the usual sulfonamide toxic effects. It was a happy day for the pneumonia patient when sulfathiazole came on the scene, to be followed in a short time by sulfadiazine.^{6,7} These are the two drugs, together with their soluble sodium salts for parenteral injection, that should be used in lobar pneumonia at the present time. They are as effective as any of the other known sulfonamides, and they produce a relatively low incidence of toxic reactions. Of the two, we favor sulfadiazine because we believe it to be less toxic, and the blood concentrations following its administration are more satisfactory. There remains room for argument over the choice between sulfathiazole and sulfadiazine, but in this country there is no longer excuse for the use of sulfanilamide or sulfapyridine in lobar pneumonia.

Recently three new sulfonamides have been reported on—sulfapyrazine,⁸ sulfamerazine,⁹ and sulfamethazine.¹⁰ Chemically, they are closely related to sulfadiazine. In sulfapyrazine the substituted heterocyclic ring is an isomer (same atoms differently arranged) of the pyrimidine ring of sulfadiazine. In sulfamerazine and sulfamethazine the structure of the ring is identical with that of sulfadiazine, but in the merazine one hydrogen atom is replaced by a methyl (CH_3) group, and in the methazine two hydrogen atoms are each replaced by a methyl group. Experi-

ments show that these three new drugs have about the same bacteriostatic effect upon the pneumococcus as does sulfadiazine, and the clinical reports, although they include too few cases to be conclusive, indicate that the curative power is of about the same order. Pharmacologic studies, however, reveal rather marked differences in these diazine derivatives. Sulfapyrazine is more slowly absorbed and excreted than are the other three. The drug is retained in the blood for a longer time and the average concentration in the blood after similar dosage is lower. Sulfamerazine, on the other hand, because of differences in absorption, excretion, and distribution gives much higher blood levels than do the others following a standard dosage. Sulfadiazine has an advantage over the others in its consistently low acetylation. Each of the other three shows in some instances a sufficiently high degree of acetylation with a corresponding decrease in the free and active portion for the treatment on this basis to become ineffective. Serious toxic reactions may occur also in these cases of high acetylation.

Sulfadiazine, in our estimation, has a further advantage over the recently reported derivatives. All of these drugs, both in their free and acetylated forms, have low solubilities, and because of this, under some circumstances, are precipitated to an extent in the kidneys during excretion, thereby producing varying degrees of renal involvement. This reaction can be partially or entirely prevented by alkali therapy because these insoluble sulfonamide compounds show an increasing solubility with the rising pH within the physiological pH range of urine. This solubility curve for acetylsulfadiazine appears to us to be more favorable than that of the other acetyl compounds of the currently investigated sulfonamides.

This leads me to a discussion of the toxic reactions following the sulfonamides. At The New York Hospital we have had a particularly large experience with sulfadiazine in the treatment of a variety of infections. Recently Charles Wheeler and I¹¹ analyzed the records and tabulated the toxic reactions that occurred in 1357 hospital patients treated with sulfadiazine and/or sodium sulfadiazine. In the entire group there was one fatal reaction, a case of thrombocytopenic purpura. One hundred and twenty-one, or 8.9 per cent, of the 1357 cases showed toxic manifestations. The corollary of this—that 1236, or 91 per cent, had no recognized evidence of toxicity—is a much more encouraging method of presenting these figures. Renal irritation was the most common

TABLE II

TOXIC REACTIONS AFTER SULFADIAZINE THERAPY—1357 CASES*

| | | |
|------------------------------------|-----|------|
| Renal Reaction | 58 | |
| Renal Reaction with Fever | 2 | 4.6% |
| Renal Reaction with Fever and Rash | 3 | |
| Drug Rash and Fever | 19 | |
| Drug Rash with Leukopenia | 1 | 1.8% |
| Drug Rash with Peripheral Neuritis | 1 | |
| Drug Rash with Stomatitis | 1 | |
| Leukopenia and/or Granulocytopenia | 15 | 1.1% |
| Drug Fever alone | 4 | |
| Nausea and Vomiting | 9 | |
| Thrombocytopenia | 1† | |
| Jaundice—possible hepatitis | 2 | |
| Conjunctivitis | 1 | |
| Stomatitis | 1 | |
| Headache and Vertigo | 1 | |
| Encephalopathy | 1 | |
| Arthralgia | 1 | |
| Total patients with reactions | 121 | 8.9% |

* From Plummer and Wheeler.¹¹

† Fatal reaction.

reaction, occurring in 63, or 4.6 per cent, of the cases. Drug rash occurred in 1.8 per cent of the patients, and this is a very low incidence as compared with that reported after sulfathiazole and sulfanilamide. Leukopenia, in no case severe, was detected in 15 instances. Agranulocytosis or hemolytic anemia did not occur in the series. Drug fever alone developed in only 4 patients, and although fever was present also in most of the patients who had toxic rashes, this again was of rare occurrence as compared with that following the use of other sulfonamides. In the patients who had previous sulfonamide therapy, a slight increase in reactions was observed, although this was not nearly so great as might be expected from recent reports on sulfonamide sensitization. Following intravenous administration of sodium sulfadiazine, the total incidence of reactions was higher because of a doubling in the number of renal reactions.

It is evident from our analysis that sulfadiazine produces less toxicity than do any of the other sulfonamides that have been extensively used, but that the renal reaction has offered a serious and relatively frequent consequence of its use. Fortunately, by the use of proper adjuvant alkali therapy we have found the means of preventing this complication.¹² This type of renal reaction was first discovered following the use of sulfapyridine; it occurred with sulfathiazole, and is now known to follow sulfadiazine as well as each of the three new derivatives. If no alkali therapy is used, following the use of all of the sulfonamides, except sulfanilamide, a proportion of the urines show sulfonamide crystals. These are almost always the acetyl compounds, except after intravenous treatment when either the free and/or acetylated forms are commonly found. Furthermore, concretions and crystals which have been recovered directly from the kidney at postmortem examination have been found on chemical analysis to be largely acetyl sulfonamide. Because theoretically it seemed to us that the deposition of crystals in the kidneys and the resulting reactions were largely dependent upon the extent to which they dissolved in the urine, we were led to ascertain accurately the solubility of each drug at pH levels throughout the physiological range of urine. This investigation undoubtedly would have been carried out earlier had it not been demonstrated clinically that alkalization of the urine was of no value in preventing the renal complications of sulfapyridine.

When the solubility figures of the various sulfonamides and their acetyl derivatives are examined,¹² the explanation for the failure of alkali to prevent sulfapyridine reactions is evident. It is also readily seen that the sulfapyridine curves are much different from those of the other sulfonamides. Both the free and combined sulfapyridine have approximately the same solubility at pH 7.5 as at pH 5.5. Sulfathiazole shows an increasing solubility, and acetylsulfathiazole is four times as soluble in an alkaline urine as in an acid one. However, this is a particularly insoluble compound, and at pH 7.5 it reaches only 28 mg. per cent. Acetylsulfadiazine rises from 20 mg. per cent solubility at pH 5.5 to 512 mg. per cent at pH 7.5, and this we believe explains the excellent prophylactic results obtained when sulfadiazine is accompanied by adjuvant alkali therapy. It is to be noted that sulfamerazine, sulfamethazine, and sulfapyrazine, and all of their acetyl compounds are more soluble at the higher pH levels, suggesting that alkalis should be adminis-

TABLE III

SOLUBILITIES IN MILLIGRAMS PER CENT OF VARIOUS SULFONAMIDES AND THEIR N₄-ACETYL DERIVATIVES AT DIFFERENT pH LEVELS*

| Compound | pH Levels | | |
|----------------------------|-----------|-----|-----|
| | 5.5 | 6.5 | 7.5 |
| Sulfapyridine | 61 | 61 | 62 |
| Acetylsulfapyridine | 33 | 34 | 37 |
| Sulfathiazole | 98 | 108 | 235 |
| Acetylsulfathiazole | 7 | 9 | 28 |
| Sulfadiazine | 13 | 28 | 200 |
| Acetylsulfadiazine | 20 | 75 | 512 |
| Sulfamerazine | 35 | 45 | 170 |
| Acetylsulfamerazine | 38 | 57 | 272 |
| Sulfamethazine | 69 | 76 | 140 |
| Acetylsulfamethazine | 90 | 107 | 240 |
| Sulfapyrazine | 4 | 10 | 65 |
| Acetylsulfapyrazine | 8 | 45 | 170 |

* From Gilligan et al.¹²

tered with each of these drugs. At a pH of 7.5, acetylsulfadiazine is the most soluble of the acetyl derivatives. From this it can be reasoned that, if the urine is kept alkaline, sulfadiazine is the safest drug; on the other hand, in acid urine acetylsulfamethazine is the most soluble, but this advantage is probably offset by the greater acetylation following the use of sulfamethazine.

Clinical studies¹² that followed our chemical determinations have shown that crystalluria and evidences of renal damage or urinary-tract obstruction are not encountered after the usual dosage of sulfadiazine or sodium sulfadiazine when the urine is maintained neutral or alkaline during treatment. The urine in patients receiving sulfadiazine but no alkali is almost always acid and we have found that about 15 gm. of sodium bicarbonate daily is required to produce the desired alkalinity. We have also found that this amount of alkali can be administered without evidence of alkalosis. At the present time, with sodium sulfadiazine we are using sixth molar sodium lactate solution, about 1,000 cc. daily. While it is evident from the solubility curves that alkali therapy is also indicated when sulfathiazole is used, whether crystalluria and renal complications can again be completely prevented has not been ascertained.

Because of the low solubility of acetylsulfathiazole throughout the pH range of urine, one would predict that it would not be possible to prevent the precipitation of crystals. In the past with sulfonamide therapy, attempts have been made to prevent the renal reactions by giving a high fluid intake. Undoubtedly this has been partially successful, but the inefficacy of this method as compared with alkalization can be emphasized by pointing out that increasing the fluid intake twofold can only double the amount of acetylsulfadiazine dissolved, whereas raising the urine pH from 5.5 to 7.5 will increase its solubility more than 25 times.

I have already indicated that in the sulfonamide treatment of pneumonia, sulfadiazine and possibly sulfathiazole are the drugs to use and that alkalis should always accompany them and that this should not be 10 grains every 4 hours, but an amount that will ensure a neutral or alkaline urine. There is one other phase of sulfonamide therapy that I wish to discuss, and that is dosage of drug. I believe it has been conclusively demonstrated that the incidence of toxic reactions from the sulfonamides is directly proportionate to the size of the daily dosage and to the duration of treatment.¹¹ On the other hand, although there is evidence from animal studies that the protective power of the sulfonamides rises until the concentration reaches 3 to 4 mg. per cent, there is little evidence, experimental or clinical, that higher concentrations have greater value. Furthermore, the response to the sulfonamides in almost all cases is rapid and not slow and drawn out. Even in such resistant conditions as subacute bacterial endocarditis, in our experience when we have had success it has been with a relatively low dosage of drug and improvement has occurred in a short time.

Dowling and his coworkers¹³ recently reported the treatment of alternate pneumonias with a daily dosage of 3.0 and 6.0 grams of sulfadiazine. They found no increase in the mortality or complications when the smaller dosage was used, but the recovery of the patients was not so rapid. Their findings and a somewhat similar experience of our own suggests to us that 3.0 gm. of sulfadiazine daily to an adult patient is near the minimal effective dose, and that a slightly higher one is preferable. We have had experience with daily dosages of both 4 and 5 grams and have no reason to believe that the patients did not respond as well as they did with the higher amounts. My own recommendation has been 1.0 gram every 4 hours, cutting the 4 a.m. or another of the night treat-

ments. The duration of treatment naturally varies with a number of circumstances, but to continue the drug for 48 to 72 hours after the temperature has reached normal is being conservative enough. One of the chief mistakes that we have observed has been the continuation of sulfonamide therapy for long periods when there has been no sign of a response. Particularly is this seen in cases of primary atypical pneumonia. To be sure, frequently a trial with sulfonamides is indicated when the diagnosis is not definite, but 48 to 72 hours is sufficient for this trial period, and to continue it longer gives too large a chance for a severe toxic reaction that could be avoided. Previously I mentioned the greater hazard of intravenous sodium sulfadiazine, and because of this we are limiting its use to the few patients who cannot take sulfadiazine orally and the occasional critical case where it is imperative to establish a blood concentration immediately.

When Bullowa,¹⁴ who has been such a great leader in pneumonia investigation, wrote his book on this disease a number of years ago, he indicated by its title that the proper and modern care was management, not just treatment. There are many important details in the care of the pneumonia patient not strictly therapeutic, but diagnostic, upon which correct therapy, however, is based. I should like briefly to outline these guides by which the correct diagnosis is established, and by which the development of complications and toxic reactions is promptly recognized. It should be pointed out that at least 85 per cent of the patients having pneumococcus pneumonia will recover satisfactorily if they are put to bed and given adequate sulfonamide treatment. Undoubtedly the most important reason today for the apparently low incidence of pneumonia is that many patients receive the sulfonamides in the very early stages of the disease, in some cases before the secondary infection following a cold has progressed to the stage of pneumonia, and the true nature of the infection is never known. This type of therapy is, of course, all to the good, and no longer can a physician be criticized for treating such a case without knowing the result of sputum typing and blood culture study. These patients need very little laboratory work-up. A blood count, at least a carefully examined blood smear, and a urine analysis should always be made at the time that the sulfonamides are commenced. This small amount of laboratory work will usually suffice in these cases of questionable and aborted pneumonia.

Beyond these cases are those not recognized until they have the

TABLE IV

GUIDES TO TREATMENT

-
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1. Careful daily observation of signs and symptoms, including gross inspection of urine.
 2. Blood counts.
 3. Urine analyses.
 4. Sputum typing and blood culture study.
 5. Blood chemistry. Blood level of drug.
-
-

frank disease together with those that develop complications, resistant infections, and toxic reactions. These pneumonias represent so-called medical emergencies; they require the closest attention with many laboratory check-ups, and they usually are much better off in the hospital. The most serious error today is to put too much confidence in the sulfonamides and, because of this, to overlook the occurrence of complications, sulfonamide resistance, or toxic reactions until it is too late.

The important guides to remember are the following:

1. *Careful daily observation of signs and symptoms, including gross inspection of the urine.* This is important, and if carried out carefully and conscientiously it is rare that a complication will be overlooked.

2. *Blood counts.* The recommendation of a blood count at the start of therapy has already been made. In addition to its value in recognizing complications and toxic reactions, it is a particular aid in differentiating between lobar and atypical pneumonia.

3. *Urine analysis.* This should be done when the sulfonamides are started because cases of renal disease require special consideration. The determination of the pH of the urine is the check on alkali therapy and should always be made when the sulfonamides are being administered.

4. *Sputum typing and blood culture.* These tests should be carried out in any patient who when first seen has respiratory symptoms and is critically ill. In addition, they should be made in patients not improving at the end of 24 hours of sulfonamide therapy. It is a mistaken notion that pneumococcal typing cannot be done after sulfonamides have been used. When sulfonamide resistance is suspected, the bacteriological study should include also a test of the organism isolated for drug sensitivity.

5. *Blood chemistry. Blood level of drug.* Whenever kidney disease is suspected, blood-chemistry determinations as an index of renal function should be made at the start of sulfonamide therapy and repeated as indicated. The blood level of drug should be ascertained whenever the response is not satisfactory or there is evidence of toxicity and again should be repeated, depending upon the indications.

Finally, I shall give you a base-line for comparison with what your next speaker will tell you about penicillin, by briefly summarizing the results in lobar pneumonia which can be expected following correct management and prompt and adequate use of the sulfonamides. The *recovery rate* will be high, with a miraculous response in a few of the cases that already have the most serious complications such as terminal septicemia or meningitis, or have advanced almost to a moribund state. Most of the fatalities will occur either in these cases of advanced disease or in those with serious associated systemic disease. The *course* in the uncomplicated case will be short, usually with the temperature normal in 24 to 48 hours after commencement of specific therapy. *Complications* following early therapy will be rare. *Sulfonamide-resistant infections* will be encountered in about 2 to 3 per cent of the cases. *Toxic reactions*, if sulfadiazine in proper dosage and adjuvant alkali therapy are used, will occur in less than 5 per cent of the cases.

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THE MODERN TREATMENT OF PEPTIC ULCER *

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INTRODUCTION

A COMPREHENSIVE discussion of the modern medical and surgical therapy of peptic ulcer in the allotted time is indeed a formidable task. An attempt will be made, therefore, to present this large and complex subject in a concise but critical fashion. The opinions expressed here tonight are the result of 20 years of concentrated experience with peptic ulcer patients.

BASIC CONSIDERATIONS

A number of basic considerations in this field are enumerated. (Table I).

A brief review of the more important modern ulcer therapies will now be presented. Table II reveals in outline form most of the modern therapies for peptic ulcer. Obviously, it will be impractical to discuss each one. I shall however, make a few critical remarks about the more important modern ulcer therapies.

The Einhorn Treatment. This treatment consists of tube feedings into the duodenum aimed to lessen mechanical irritation of the ulcer. This is accomplished but unfortunately it is very stimulating to acid secretion. Today it is generally considered unphysiologic and is therefore used very little.

Henning Therapy. Henning passed the thin tube deep into the jejunum. He claimed that intrajejunal feeding does not stimulate gastric secretion but will prevent trauma of the ulcer. However, we have found that it does not stop the continuous nervous hyper-secretion. Also, it causes in many cases uncontrollable diarrheas. For these reasons, it has not become popular.

* Read October 13, 1943 in the Sixteenth Graduate Fortnight of The New York Academy of Medicine.

TABLE I

1. The etiology of peptic ulcer is as yet unknown
2. Ulcer is probably not a unitary disease etiologically
3. The psychosomatic and "constitutional" theories are prominent today as ultimate causes
4. The immediate mechanism is acid (or acid-pepsin) acting on susceptible mucosal sites
5. Therefore, general and local therapeutic attacks are both desirable
6. The pathological state of the individual ulcer and the gastric mucosa is of greatest importance in therapy
7. The acute ulcer is a medical disease
8. The acute ulcer has the best chance of complete and permanent cure
9. The chronic uncomplicated ulcer is also a medical disease
10. It is characterized by spontaneous remissions
11. There are two main types of ulcer life-cycles: Type *I*. Long histories with short remissions; Type *II*. Long histories with long remissions
12. Type *I* is rarely cured medically
13. Medical cures are also rare in:
 - (a) hour-glass stomachs
 - (b) progressive deep penetrations
 - (c) organic pyloric obstructions, and
 - (d) duodenal pseudo-diverticula
14. Ulcer symptoms are easily influenced (hence a variety of therapies has arisen)
15. Loss of symptoms with any of these does not necessarily constitute cure
16. Ulcer life-cycles must be interpreted in relation to individual sensitivity
17. Chronic ulcers without symptoms ("latent") are common
18. Chronic peptic ulcer is a lifelong disease
19. Ulcer in the female is milder, less frequent, less complicated and more easily cured
20. Duodenal ulcer niches are always benign
21. Gastric ulcer niches should be considered malignant until proved benign
22. I agree with Arthur F. Chace, who said in his gastrointestinal Fortnight Lecture in 1934: "Recurrences are the central problem in ulcers and are often due to a failure to persist in ulcer therapy for long periods, if not for a lifetime."
23. Remediable causes of recurrences are dietetic, emotional, alcohol, tobacco and fatigue
24. Non-preventable causes of recurrence are spontaneous, seasonal, infectious, and the menopause
25. Only a small per cent of ulcers are cured medically; a fair per cent go through life with mild symptoms; the remainder (25 per cent?) are refractory and require intensive therapy either medical or surgical.

TABLE II

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1. DIETETIC THERAPIES
 - a. Lenhartz-Leube
 - b. High protein
 - c. High vitamin
 - d. Sauerbruch-Hermannsdorfer
 2. DEFICIENCY THERAPIES
 - a. High protein and histidin
 - b. Vitamins (C)
 - c. Parathyroid extract
 3. PROTECTIVE BY-PASSING OF THE STOMACH
 - a. Einhorn therapy
 - b. Henning-Bockus intrajejunal feeding
 4. ACID NEUTRALIZATION THERAPIES
 - a. Absorbable alkalis
 - b. Sippy "cure"
 - c. Non-absorbable alkalis
 5. PARENTERAL FOREIGN PROTEIN THERAPY
 6. RADIOTHERAPY
 7. INSULIN
 8. PSYCHOTHERAPY
 9. ATROPINE
 10. MUCIN
 11. LIVER EXTRACT
-
-

The Sippy Cure. The Sippy "neutralization cure" is based on frequent hourly feedings to adsorb and dilute the acid and on the intake of large doses of absorbable alkalis to neutralize the gastric acidity. There is admittedly often a rapid loss of symptoms, but, as already pointed out, that does not necessarily mean healing. The bad features of the Sippy therapy are (1) the huge amounts of absorbable alkali employed and (2) bodily alkalosis as a result with many untoward symptoms; (3) it does not accomplish a neutralization to the desired end-point between the meals (Palmer, Hurst, Winkelstein); (4) it does not control the nocturnal hypersecretion of ulcer patients; (5) it requires hospital or home confinement; (6) the diet is increased too gradually for adequate tissue nutrition; (7) recurrences are the rule; (8) finally, there is no proof that the Sippy treatment produces quicker healing or even longer remissions than other more convenient therapies. In my opinion, the widespread use of this therapy is not justified, either theoretically or practically.

Non-absorbable Alkalies. Non-absorbable alkali therapy using chiefly the alumina gels (aluminum hydroxide and phosphate) mark an advance in ulcer therapy. They neutralize large amounts of acid without inducing a bodily alkalosis. The astringent and pepsin-absorbing features are also of value. Despite the inconvenient liquid form and the constipating action, the clinical evidence favors their use.

Parenteral Foreign Protein Therapy. Parenteral foreign protein therapy using milk, lipo-vaccines, activin, synodal, larostidin, or pepsin, do relieve pain in a small per cent of refractory cases. Theoretically this therapy is used to combat infection or to induce a beneficial local hyperemic effect on the lesion. It is highly probable that the effect is largely psychologic since E. Granet in our clinic obtained an equally good effect from sterile saline injections. In my opinion this form of therapy should be dropped.

Psychotherapy. The proponents of psychotherapy present the following arguments: (1) ulcer patients are profoundly neurotic; (2) emotional disturbances frequently precipitate recurrences; (3) psychic improvement helps ulcer patients; (4) the evocation of the neurotic disturbance in the consciousness induces a gastric hypersecretion and vascular spasm; (5) in periods of stress and strain, as in World War II, ulcer incidence increases markedly.

While there is today a general tendency to regard and treat young adult ulcer patients as neuroses, certain considerations arise:

1. Why, if ulcer is a neurosis, is it predominantly a male disease?
2. A specific type of neurosis affecting only or preferentially the stomach has not yet been described.
3. Control series for psychotherapy versus drug-diet therapy and for the psycho-physiologic experiments are desirable.

Finally, while it does seem probable that peptic ulcer is very often a psychosomatic disease it is well to bear in mind that peptic ulcer may not be a unitary disease and may even require a constellation of factors to produce it.

Atropine Therapy. Atropine or belladonna therapy is of great value. It inhibits the characteristically excessive vagus nerve secretion and lessens the excessive motor activities. Its effect is enhanced by the concomitant use of sedatives. Given before meals, both secretory and motor factors are lessened. In my opinion, atropine is, theoretically and practically, an essential part of any ulcer therapy.

Mucin Therapy. A modern ulcer therapy that attracted a great deal of attention—at least for a time—was the mucin therapy. It was based on the deficiency idea plus mechanical protection, acid neutralization, and pepsin adsorption. Unfortunately, the commercial products, obtained from the hog's stomach, apparently contained powerful secretagogues. In view of this, its disagreeable taste, and lack of clinical evidence to support it, this type of therapy soon fell into disrepute. However, the fundamental idea that increased mucus produced locally would be of value in the treatment of peptic ulcer is plausible. Methods of stimulating gastric mucus should be sought. The problem of mucus deficiency is also well worth studying.

Erosive antrum gastritis and duodenitis. In view of the fact that erosive antrum gastritis and duodenitis is so commonly associated with peptic ulcer, part of our therapy should be directed against it. In my personal experience, liver extract injections are of real value in this connection. In analogy to its effect on the so-called "gastritis" of pernicious anemia, liver extract may act by containing some substance which helps to preserve and restore the integrity of the gastric mucosa.

I shall now summarize what I consider the best medical therapy to date:

1. A liberal bland "ulcer" diet with increased protein and vitamin intake.
2. Atropine or belladonna plus phenobarbital a.c.
3. Alumina gels. p.c.
4. A hot saline laxative on arising and mineral oil at night.
5. In-bed therapy for three or four weeks.
6. Psychotherapy.

The adjuvants of value are:

1. Moist heat to the abdomen.
2. Liver extract injections.
3. Gastric lavage.

PART III

Despite the good features just pointed out, there has arisen a general dissatisfaction with the conventional modern ulcer therapies for the following reasons:

1. Most of them temporarily relieve the symptoms but do not cure the ulcer, or rather, the "ulcer patient" permanently.

2. They are inconvenient, for example, the hourly feedings of the Sippy treatment.

3. They do not neutralize the interdigestive and night acid secretion.

4. Recurrences are the rule and complications often set in.

5. The economical loss is great.

What, then, we may ask, constitutes an adequate or ideal ulcer therapy? An adequate ulcer therapy should:

1. Neutralize the free acidity between the meals and during the night (to stop symptoms and promote healing).

2. Allay excessive motor activities (to stop vascular spasm, pylorospasm and mechanical injury).

3. Result in an optimum motility (without gastric retention and yet no dumping action in the duodenum).

4. Attack distant and reflex harmful states such as neuroses, infections, allergies, constipation, and other organic diseases.

Obviously, none of the ulcer therapies described to this point fulfills the criteria of an "adequate ulcer therapy."

PART IV

In 1931, I developed in The Mount Sinai Hospital a new therapy which seemed more logical and offered promise of better results in the medical therapy of peptic ulcer. That treatment may be briefly defined and described as a "local intubation ulcer therapy based on the principle of a continuous, adequate, intragastric neutralization of the free hydrochloric acid between the meals and during the night by a milk-soda drip."

The idea of using a drip therapy between the meals and during the night arose as a result of the following considerations:

1. The Sippy therapy fails to control the acidity during the day.

2. There is a very marked hyperchlorhydria and hypersecretion during the night in ulcer patients.

3. This nocturnal acid secretion is very high despite Sippy therapy during the day.

4. Also, the high nocturnal secretion persists despite various measures before retiring such as complete aspiration, alkalies, olive oil, atropine and sedatives.

5. The Sippy therapy frequently fails to control the night symp-

toms of ulcer patients.

6. Finally, if, as is generally held, the sine qua non of ulcer healing is a continuous achlorhydria, it is folly to try to control the acid during the day and not during the night.

Certain *basic physiologic studies* have been carried out in patients in collaboration with Cornell and Hollander, which demonstrate the efficacy of the interdigestive and night drip in controlling the gastric acidity. A summary of our studies reveals the following:

1. The curves of gastric acidity in duodenal ulcer patients between the meals and during the night average a pH of 1.2 to 1.3 or about 60 to 80 clinical units.

2. Milk-soda mixture and its modification, using diluted alumina gels (diluted in water or milk) dripped into the stomach establish a pH of 3.5 to 4 between the meals and during the night. At this point, there is an essential absence of free hydrochloric acid and an almost complete absence of peptic digestion. Thus, with our therapy, we attain the ideal gastric milieu for healing.

During ten years of experience with the drip therapy, certain practical points have arisen:

1. The apparatus is simple and inexpensive.

2. The technique is quickly learned so that nearly all the patients can administer it to themselves at home during the night.

3. Ulcer patients do not find it a drastic or difficult method since most of them are "tube broken."

4. Mild cases treat themselves only during the night.

5. Moderate and severe cases employ it between the meals and during the night.

6. Continuous 24 hour drip therapy is rarely necessary.

7. Three liberal bland "ulcer" meals with atropine plus phenobarbital a.c. and an aluminum gel p. c., plus the interdigestive drip permits maximum tissue nutrition and provides an optimal neutralization.

8. It may be used for long periods of time at home during the night and thus the patient undergoes an ideal ulcer cure while sleeping and, also, without interference with his daily earning capacity.

9. Milk-soda drip and alumina gel drips are not rivals but are complementary. The alumina gels, for example, are of great value when milk sensitiveness exists or bodily alkalosis threatens.

The question next arises as to how efficient the drip therapy is in

the actual treatment of ulcer patients. I have been impressed, in an experience with several hundred patients, by the following:

1. There is a rapid loss of symptoms, usually within a few hours.
2. Ulcer niches heal rapidly; huge gastric ulcer craters have disappeared in 19 days.
3. We have seen very long remissions after this form of therapy.
4. It is definitely the best method of controlling the distressing night symptoms of ulcer.
5. It works frequently when the conventional Sippy therapy fails. We are reporting separately, in detail, a series of 60 ulcer patients who were refractory to Sippy but responded to the drip therapy.
6. It has, therefore, helped to avoid surgical therapy in a considerable number of cases.

Finally, what may we conclude concerning the intragastric drip therapy? After ten years' experience we are convinced that:

1. It is based on the logical principle of continuous neutralization.
2. It is practical.
3. The results are better than with previous ulcer therapies and justify it as a "new" ulcer therapy.
4. The Sippy therapy, now the most widely used therapy for uncomplicated peptic ulcer, should be discarded in its favor whenever practical.
5. Every patient with uncomplicated ulcer should learn and use this therapy.
6. An extensive trial of it should be made not only in civilian but also in military life.
7. In the present World War, peptic ulcer looms large as a cause of medical disability.
8. In the previous World War the "nervous heart" or so called neuro-circulatory asthenia ("n.c.a.") was the important medical disease; whereas in this conflict it seems to be peptic ulcer. The reason for this is conjectural. Whether it is the diet; whether it is the terrific, smoldering resentment against Nazi atrocities as yet unrelieved by actual combat; whether it is tension as a result of ambition, discipline, or fear; whether it is a lighting up of a previous ulcer; or, whether it is a separation from a comforting and supporting home environment; cannot as yet be decided. In any case, it is my personal experience that any young man who has or has had a definite peptic ulcer or even characteristic

ulcer symptoms will, under military conditions, suffer from a recurrence of his symptoms. It is then a question as to whether a military discharge is imperative. We would like to suggest that men who are of special value to the service, such as officers, administrators, pilots, etc. should be treated thoroughly in the military hospitals in an effort to obtain a long remission.

The use of an intensive therapy like the drip treatment at night in military hospitals for several weeks probably would, in our opinion, restore many useful men to active military duty.

It should be emphasized that draft boards should definitely not accept for military service men with proved peptic ulcer, past or present.

9. A final point may be made before leaving the subject of the drip therapy. While we feel that the drip therapy is a definite advance in the medical therapy of ulcer, no claim is made for this therapy as a complete, general therapy of the ulcer disease in the ulcer individual. That ideal therapy must await the final discovery of the true etiology of ulcer.

10. Additional concomitant therapeutic measures are therefore desirable and necessary, viz: psychotherapy, rest, vacations, and removal of toxic and reflex foci of irritation.

PART V. SURGICAL THERAPY

No discussion of the modern therapy of peptic ulcer would be complete without a consideration of some aspects of the modern surgical therapy. A few basic considerations will be mentioned first.

1. Ulcer per se is not a surgical disease.
2. Neither a long history nor a large crater is an indication for surgery.
3. A Roentgen-invisible ulcer is not a surgical ulcer.
4. However, the following situations *are* indications for surgery and should be strictly heeded by the practitioner.
 - a. Open, sealed-off, or threatened perforation.
 - b. Pyloric obstruction, hour-glass stomach, and duodenal pseudo-diverticula.
 - c. Progressive penetration.
 - d. Repeated massive hemorrhages in the interval stage.
 - e. A combination of a long history, short remissions and refrac-

toriness to adequate medical therapy (especially drip therapy).

f. Suspicion of malignancy. Every gastric niche should be considered malignant until proved benign. A niche which enlarges while on adequate medical therapy is suspicious. Very large niches suggest neoplasm. However, very small niches may also be ulcerated carcinomas. Progressive anemia, asthenia, constant occult blood, and loss of free acid are all suggestive. Gastroscoy may help. The carcinomatous degeneration of a benign ulcer is rare. However, the differential diagnosis of a benign ulcer from an ulcerated carcinoma may be extremely difficult. A new diagnostic method, perhaps chemical, is sorely needed here.

With reference to the type of surgical therapy for peptic ulcer. I have arrived at the following conclusions:

1. An ideal surgical therapy removes the ulcer; removes the associated gastritis; removes the ulcer-bearing area; abolishes the free acid; gives an optimum motility; and, finally, and, most important, prevents recurrences.

2. Gastroenterostomy fails in most of these basic requirements and, especially because of the terrifically high incidence of recurrent jejunal ulcers, should be given up whenever practical.

3. After considerable resistance, the time-honored procedure of gastroenterostomy is being given up and partial gastrectomy is today the operation of choice.

4. The mortality of partial gastrectomy in experienced hands is not too high (2.5 to 3 per cent).

5. After partial gastrectomy, there is a postoperative achlorhydria in practically 100 per cent of gastric ulcers at the angle and in 55 per cent of the duodenal ulcers.

6. Such a postoperative achlorhydria is a guarantee, in our experience, against a recurrent ulcer.

7. Partial gastrectomy is, therefore, a permanent cure for angle gastric ulcers; partial gastrectomy is also a cure for 55 per cent of duodenal ulcers.

8. Recurrent jejunal ulcers are not rare after partial gastrectomy for duodenal ulcer with a high preoperative free acidity and with retained postoperative free acidity.

9. However, even here, the incidence of recurrence is only one third of the incidence after gastroenterostomy.

The greatest problem in the surgery of peptic ulcer today is to prevent these recurrences after partial gastrectomy for duodenal ulcer. While it seems quite true that there exists a group of ulcer patients who seem to be incurable surgically, we have felt that if it were possible to obtain a postoperative achlorhydria in all of the duodenal ulcer patients we could avoid a recurrence.

I have therefore directed my attention to the problem of the persistent free acidity after partial gastrectomy in 45 per cent of the duodenal ulcer patients. This acidity is presumably responsible for the recurrent ulcers. My studies indicate the following:

1. The high acidity in this group of duodenal ulcers is due to an excessive vagus nerve phase of gastric secretion.
2. Atropine abolishes this postoperative secretion.
3. Therefore, for these two reasons, the addition of vagus nerve section suggested itself.
4. Anterior subphrenic vagotomy is a simple, harmless procedure and theoretically abolishes one-half of the vagal secretion.
5. This, plus antrumectomy, jejunal regurgitation, and postoperative gastritis is sufficient to produce a postoperative achlorhydria in most of the cases.
6. This easy procedure has been carried out by Berg in thirty-four patients with duodenal ulcer with a very high preoperative acidity.
7. Twenty-six of the thirty-four patients revealed a postoperative achlorhydria. These patients have been followed for five to ten years and no recurrences have been noted.
8. Since recurrent jejunal ulcer occurs most frequently in the group of duodenal ulcers with a high preoperative acidity, the addition of the vagotomy to the partial gastrectomy, leading to achlorhydria in most cases, seems to be a valuable addition to the surgical therapy of peptic ulcer and is strongly advocated as a result of my experience.

CONCLUSION

In conclusion, a few hints about the possible future therapy of peptic ulcer may not be amiss. If ulcer is really a neurosis, psychotherapy should engage our attention closely. In the local therapy, methods of instituting a harmless, chronic achlorhydria by simple medical means should be sought for by our research fellows. Whether gastric mucus or enterogastrone will be a panacea is conjectural. A group of meno-

pause ulcer cases relieved by estrogen therapy indicates a ductless glandular factor at least in one group of ulcer patients. Intrajejunal feeding plus interdigestive intragastric drip should be studied as a novel but logical cure in this connection.

Finally, a few words about *ulcer prophylaxis* are indicated. Experience shows that the shorter the ulcer history the more chance there is of a complete and permanent anatomic and clinical cure.

It is therefore the duty of the general practitioners to recognize the disease early and to treat it at that period most intensively. The analogy to incipient pulmonary tuberculosis is obvious. Hence my plea for the more rigorous drip therapy even in the earliest and mildest cases. Perhaps we would then achieve a more gratifying result with medical therapy.

Chronic peptic ulcer of years' duration is usually an incurable, recurrent and often disabling disease. Such patients require a radical revision of their entire life programs and continuous general and local ulcer therapy as broadly outlined here tonight.

DIGESTIVE TRACT DISTURBANCES IN RELATION TO RECTAL AND ANAL CONDITIONS *

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INASMUCH as this symposium is concerned with disturbance of the alimentary tract, we shall omit certain conditions, such as pilonidal sinus and pruritis ani, that have little or no relation to digestive functions. On the other hand, emphasis will be placed on digestive disturbances that may cause rectal and anal conditions, and conversely lesions in this group that may give rise to digestive symptoms. Frequently the reciprocal relationship is such that it is difficult to say what is cause and what is effect. For instance, consider the question of constipation as concerns rectal lesions. There is a widespread belief that constipation is one of the factors that may cause hemorrhoids, fissure, and at times abscess and fistula, and undoubtedly there is considerable truth in this belief. Hemorrhoids may be caused by various conditions, such as pregnancy, pelvic tumors, cirrhosis of the liver, that produce stasis and congestion in the hemorrhoidal plexus of veins. Among these conditions chronic constipation with straining at stool certainly finds a place, yet it is true that many patients with well developed hemorrhoids give no history of constipation. Injury to the rectal and anal structures from the passage of hard stool is probably the commonest cause of fissure in ano, and is a occasional cause of perirectal abscess and fistula. The advanced form of constipation that results in fecal impaction gives rise to rectal pressure, tenesmus and a hard mass that may be mistaken for carcinoma.

The reverse relation may be illustrated best by fissure in ano. The severe pain of fissure, with associated sphincter spasm, is usually precipitated by bowel movement. The patient soon learns this and often voluntarily tries to avoid defecation, sometimes for days together, with consequent establishment of marked constipation.

It will be seen from these illustrations that there is an intimate rela-

* Given October 21, 1943 at the Graduate Fortnight of The New York Academy of Medicine.

tion between certain functional disturbances of the alimentary tract and rectal and anal disease. For years we have taught our students to elicit certain cardinal facts in taking histories in this group of patients. We have pointed out the importance of subjective symptoms, such as pain, of objective findings, such as the appearance of blood, pus, or swellings, and the existence of disturbances of bowel habits. Insistence has been placed also on the time element in the history, as manifested by duration and time relation to other incidents like bowel movement. We have particularly stressed an accurate account of any alteration of defecation. It is not enough to quote the patient as saying that he suffers from constipation or diarrhea. We must ask specific questions. How many times do the bowels move in twenty-four hours? Is there any feeling of tightness or obstruction in the anal canal? Is there any protrusion that occurs with defecation? If one secures accurate answers to such questions a picture emerges that goes a long way toward helping in the diagnosis. Such interrogation is very different from the unfortunately not uncommon practice of concluding that the patient must have hemorrhoids because he casually mentions that he has passed some blood.

The occurrence of blood in the stool, visible to the patient, is one of the most frequent complaints that leads him to seek medical aid, and he usually begins his story to the doctor by asserting that he has hemorrhoids. Here again adequate questioning will often go far to providing a clue as to the actual nature of his trouble. Is the blood bright red, or dark and partly clotted? Is it frequent or only occasional? Is it profuse, moderate, or only in traces? Does it occur only with the passage of stool, or independently of such passage? Is it mixed with mucus? Does it gush out or drip? Is it mixed through the stool, or smeared on its surfaces? All of these points may be significant. The blood passed with fissure is usually occasional and scanty. Hemorrhoids often bleed profusely, usually with stool but sometimes on muscular effort, stooping, or even when walking vigorously. But it should also be remembered that old fibrous thickened hemorrhoids may not bleed at all. The bleeding of ulcerated areas in the rectum is not so apt to be profuse but is fairly constant and often is accompanied by pus and mucus. These characteristics are much the same, whether the ulceration is due to a colitis or to a sloughing new growth. Then there is the peculiar group of cases in which the patient passes a large amount of blood on a single occasion, perhaps enough to be exsanguinating, with no other symptoms. Some

of these cases, after careful and extensive study, may be explained as due to ruptured varices in the bowel wall, to ulcers in a Meckel's diverticulum, to polyps, and other lesions, but some remain a mystery in spite of all efforts to understand them. Often the bleeding never recurs and the patient remains apparently well. It will be seen from this brief discussion of the complaint of passing blood per rectum that a careful inquiry as to the facts is necessary and that snap judgments cannot be tolerated.

It is obvious, however, that simple history taking alone is only the beginning of the study of the case. There are too many quite different lesions in this field that present similar complaints. For instance, take the patient who complains of frequent urgent defecation, with passage of blood and pus. Such a story does not indicate a clinical entity; it does indicate an irritative and ulcerative lesion in the rectum or anus. Such a lesion may be as diverse in pathological nature as amebic colitis and carcinoma. It is therefore essential, when a patient presents symptoms referred to the rectum and anus, that a proper examination be carried out. This has been said many times, but must be repeated until practice conforms to precept. It has been only a few years ago that the writer saw a very prominent man with an easily detected carcinoma of the rectum which had been missed by an equally prominent diagnostician. This was not because of any remarkable ability on my part, or the lack of it on the part of the eminent diagnostician. It was due simply to failure to make an adequate digital examination. If the routine of inspection, palpation, and proctoscopic examination is conscientiously carried out, many disorders of the alimentary tract will be diagnosed that otherwise would escape recognition. Perhaps insistence upon this point before a group interested in diseases of the digestive tract is the most important contribution that I can make to the general subject.

Many of the lesions that occur in the rectal and anal region are of only *local* importance, comparatively simple in nature, and readily amenable to treatment, either medical or surgical. In this respect, one thinks of hemorrhoids, of fistula, fissure, stricture, and polyp. Yet it is not safe to generalize. I recall a young man with a profound secondary anemia, the hemoglobin being reduced to 25 per cent, entirely due to bleeding hemorrhoids and cured by surgical removal. There is the old tradition that most fistulae are tuberculous and associated with pulmonary tuberculosis. Increasing experience with large numbers of

carefully studied cases has shown that the great majority of fistulae are not tuberculous and are not related to pulmonary disease, but a few of them undoubtedly are. Fissure generally produces local disturbances only, but occasionally leads to functional general disturbance of digestion.

It may be of interest to outline briefly the author's practice in the treatment of the commoner anal and rectal conditions, not as regards details of technique but to point out certain principles. In some of these conditions the choice of a method of treatment, whether non-operative or surgical, will depend upon the circumstances of the individual case. For instance, in recent and superficial fissure cases, the use of mineral oil by mouth or some other procedure to insure soft stools, the local application of an anesthetic and healing ointment, and gentle digital dilatation, will often result in relief. On the other hand a chronic fissure, with indurated base and edges, accompanied by marked spasm of the sphincter is best dealt with by surgical removal of the lesion and forced stretching of the muscle. Similarly the treatment of hemorrhoids varies with the type of case. There are literally thousands of people who have mild anatomical hemorrhoids, that give very slight and occasional symptoms—perhaps slight bleeding and a little protrusion. These people need no active treatment, merely advice to avoid straining at stool and such exercise as may predispose to increase the trouble. Another large group have a moderate and fairly frequent amount of bleeding and at times discomfort from swelling and protrusion. In such cases, bowel hygiene, an astringent ointment, hot or cold applications, and a few days of rest and quiet, will usually control the symptoms even though the hemorrhoids remain. A third group, with thrombosis of good size, or constant protrusion or really troublesome bleeding should be operated upon without wasting time, money and suffering in useless palliative measures.

As against these conditions requiring judgment in the use of a variety of methods of treatment, certain lesions are definitely best handled by surgery, and failure to do so is generally equivalent to failure to cure the disease. True fistula in ano rarely gets well without complete and adequate surgical excision or incision, with the laying open of the tract to and including the internal orifice. The frequent apparent disappearance of the fistula without operation is nearly always temporary and illusory, as it reopens again and again. Histories of many

years of such continuous or intermittent drainage, under treatments other than operative, are very common. Another lesion requiring surgical care is polyp. These growths should be removed as soon as discovered, not only because this is the only logical treatment but because polyps in the rectum are prone to malignant degeneration. Strictures require mechanical treatment, either progressive and long continued dilatation or some form of simple plastic surgery.

Diseases of the rectum of an ulcerative nature are usually difficult to treat successfully, but the basic plan of treatment is medical. In certain cases of serious chronic ulcerative colitis, abdominal surgery is required, but this especial topic has been considered elsewhere on this program. Carcinoma of the anus and rectum is of course the major problem in this whole field. Malignant disease of the anal canal itself is usually epithelioma, and is much less common than adenocarcinoma of the rectum. Certain of these epitheliomata, like those about the face, are quite radiosensitive and respond well to radiotherapy. In cases that do so respond, and that have not yet reached a size or an extension sufficient to destroy the sphincter apparatus, the writer prefers to employ radiotherapy long enough to determine whether the disease can be cleared up by this means. Such a plan has the advantage of preserving sphincter control in favorable cases. It lacks the theoretical advantage of eliminating possible glandular extensions, and many will object to it for this reason. In epithelioma that does not prove to be radiosensitive, or that is too extensive for such treatment, radical perineal resection of the anus, sphincter, and lower rectum is required. The lymph nodes in the groins are usually the first zone of metastasis in these lesions and often should be removed surgically.

Adenocarcinoma of the rectum is a frequent occurrence and is best dealt with along the lines laid down by Mr. Ernest Miles of London in the abdominoperineal type of operation. This method involves attacking the lesion from above, through the abdomen, with division of the sigmoid, the extensive mobilization of the lower sigmoid, the upper rectum, and all the adjacent fat, fascia and lymph nodes, and the establishment of a permanent terminal colostomy of the sigmoid. The second stage of the operation consists in dissecting the rectum from the perineum upward, with removal of the perianal skin, sphincters and levators, and surrounding fat until the upper dissected field is reached. Then the whole large dissected mass is removed. Some prefer to do this

procedure in two separate operations with an interval between. Miles himself, and many others, do both parts of the operation in one sitting. It is admittedly a formidable surgical undertaking, and when first introduced was accompanied by a rather high mortality. Steady improvement in preoperative preparation, in the refinement and expedition of technique, in postoperative management, and in combatting shock have reduced the mortality to quite reasonable figures and this improvement continues. The operation is based upon sound principles of cancer surgery, and gives better late results than are now obtained in any other field of visceral cancer. It deserves the support of all surgeons.

The diseases that affect the rectum, as distinguished from the anal canal, are more commonly apt to involve general effects upon the health. This is true because some of these diseases involve not only the rectum, but often the whole colon as well, and others are of a nature that may extend to the entire body. In the first group belong the inflammatory lesions of the colitis type; in the second the malignant neoplasms. Colitis, as used clinically, is a term that comprehends certain little understood disorders that may be functional, such as so-called mucous colitis, a group of known infections due to protozoal or bacterial agents, and the remainder, that troublesome and dangerous condition which may not be a single clinical entity—known as chronic idiopathic ulcerative colitis. In most instances, proctoscopic and laboratory studies can differentiate these various forms of colitis, and serve as a guide to the adoption of appropriate methods of treatment, such as they are at present. No one will dispute that there is here a great field for improvement in our present-day therapy. For purposes of the present discussion, the points to be emphasized are that these conditions often cause preponderantly rectal symptoms, that they may be recognized by proper rectal examination, and that such examination points the way to treatment.

The second category of rectal diseases of more than local significance is the neoplastic group. There is no need to emphasize the gravity of such conditions; unless early recognized and successfully treated they end the life of the patient. It is well, however, to point out the relative frequency of carcinoma of the rectum. It shares with the stomach the questionable distinction of being the most common form of alimentary tract malignancy. It does however possess the unquestionable advantage of offering a better field for surgical attack and a more favorable prog-

nosis. These advantages depend upon easier accessibility for diagnosis, and anatomical conditions that permit wider surgical removal. To secure these advantages though, one must be alert to the possibility of such a lesion being present. So that we come back to repeat that prompt and competent examination, when rectal or anal symptoms are present, is the first obligation to the patient and the first duty of the physician.

It is obviously impossible, under the circumstances of this occasion, to cover completely the subject assigned. Whole volumes, and many of them, have been written upon it. Even a single topic under the general subject, if completely dealt with, would overrun our limitations. Take stricture for instance. Even leaving out the group of strictures due to malignancy, there are the congenital forms due to failure of normal opening of the proctodeum, the traumatic which unfortunately are in some instances a result of surgery, and the inflammatory type that includes the lymphopathia venereum infections due to a virus. Much of interest could be narrated about each of these, from the viewpoints of etiology, symptoms and treatment. Their effect upon the digestive tract, sometimes in infants resulting in megacolon, sometimes in adults causing obstruction, would be pertinent to the discussion. But detailed consideration of individual lesions would lead us much too far afield. I take it that the purpose of this paper is to renew attention to the importance of the lowliest part of the alimentary tract, to point out that it is the site of numerous disorders of both local and general importance, and that these disorders must not be lightly dismissed or overlooked in any study of the digestive organs. That a tendency to dismiss or overlook this field does exist, my personal experience leads me to believe. There is reluctance or inability of the patient to describe adequately his symptoms and to submit to examination. There is reluctance often on the part of the physician to insist upon examination or to train himself in the simple technique of making it. These factors combine to bring about a state of affairs in which diagnosis is inadequate, treatment unintelligent, and the results often unsatisfactory and sometimes tragic. It is not difficult to remedy this situation, at least so far as our present knowledge and skill permits, and the obligation to do so is very clear.

THE ROLE OF THE INTERNIST IN THE MANAGEMENT OF STERILITY*

WILLIAM H. CARY

WHEN a society primarily concerned with the problems of internal medicine devotes an evening to the consideration of the involuntarily childless marriage it must mean that this problem is making a greater impact upon a larger number of physicians. This is most gratifying. Although often neglected, medical factors, as distinguished from those involving surgical or special methods of intervention, play an important role in caring for sterility, such a classification of problems is wellnigh impossible, however, because multiple causes were noted in 53 per cent of 255 sterile marriages which I analyzed as to diagnoses and results before the Academy of Medicine several months ago.

Nearly three decades have elapsed since the speaker began what others have graciously defined as pioneer work in this field. At that time there were no landmarks and a review of the indexed literature in four languages provided no scientific criteria for interpretation or procedure. For many years after the responsibility of the male had been demonstrated in one-third of sterile unions the urologist, with very rare exceptions, held aloof from the problem and the general medical profession responded indifferently to increasing public interest. As late as 1927 my records show that of the women who had been previously operated upon for sterility, the husband had not been examined in 26 per cent of the cases and 30 per cent of these husbands were found with incompetent semen. Errors and omissions in diagnosis were frequent because scientific study of the human sexual function had been traditionally taboo and treatment of sterility was largely empirical or directed to surgical control of organic disorders. During these early years, therefore, the gynecologist especially interested in this field was compelled to evolve for himself the method and criteria for appraisal of the husband's virility and to explore all the potential causes of lowered fertility in both sexes. In later years a few gynecologists formed

* Read April 20, 1943 before the Section of Medicine of The New York Academy of Medicine.

clinical groups for such study and today most medical centers are investigating some aspect of human reproduction and younger men are being trained. It should be emphasized, however, that successful management of infertility, including adoption and the prevention of anxiety neuroses, depends upon accurately directed, competently interpreted and properly correlated diagnostic studies of the husband and wife. No single phase of research is adequate by itself and may indeed prove ridiculous in view of the mate's attitude or condition. In two of our cases wives were forced by the exigencies of the investigation to admit that they practised contraception secretly although responding to their husband's insistence that they seek special care. A perplexed gynecologist referred another patient who was reported to have become pregnant at the first premarital exposure and having married promptly after abortion had remained childless. Exhaustive investigations had been fruitless but the mystery was quickly solved when the patient admitted that the husband had not been the lover.

I appear tonight as a hybrid product of the earlier years to discuss the important role of the internist in some cases of sterility and to urge coöperation and acknowledgment of our respective limitations. As elementary examples—a professional man with unexplained physical lassitude and a defective semen which had resisted all treatment revealed confidentially to the internist, but not to the gynecologist, that he was cohabiting actively with two mistresses. From the other side of the ledger was a woman from the less-privileged class who tearfully applied for impregnation by a donor specimen and presented a letter from the social service stating that the medical attendant had misinterpreted a brief and equivocal report by a laboratory regarding the husband's semen and that the patient had invested her savings from time to time over a period of eight years for treatment, including two minor operations which had no chance of success because the husband was now known to have been sterile. Very recently I have encountered three unfortunate cases in which the wife's responsibility had been discounted and the husband unnecessarily and improperly treated because the condom, long condemned, had been used for the seminal collection.

Perfunctory diagnosis, too aggressive surgery, empiric trial of intra-uterine insemination and administration of the newer glandular products as panaceas, rather than experimental adjuncts in selected cases of infertility, do not reflect a sincere response to the yearning for parenthood.

THE MEDICAL SURVEY

We are all familiar with that elusive condition sometimes called lowered resistance and its various manifestations, such as subnormal energy, premature tiredness, nervous instability, susceptibility to infections, depressed libido and other complaints, but we may be less aware how often relative infertility is a sign of impaired health and ultimately is improved by appropriate attention to the general condition.

In male patients of this type improvement in fecundating vigor may be demonstrated after a few months by comparative evaluations of the semen but in the female we have only indirect and equivocal criteria for comparable studies. The relief of sterility after a prolonged vacation, favorable changes in living conditions, or regimes to correct metabolic abnormalities provides clinical evidence familiar to you all. In these cases of relative or functional infertility in which anatomical, developmental and organic causes have been eliminated by competent diagnostic investigation medical coöperation may be of great value. These anxious patients deserve, and their problems involve, more painstaking medical study than is sometimes manifested.

The family history should be reviewed with special reference to diabetes, glandular diseases and anomalies of the reproductive function.

Complications of vaginitis, the exanthemata, mumps, appendicitis and infantile paralysis doubtless involve the pelvic organs during childhood more frequently than is generally recognized. In my experience, vaguely remembered symptoms, when elaborated by the patient's mother, have sometimes proved significant.

ADOLESCENCE

Preëminently important in searching for causes of infertility is the adolescent history—33 per cent of the cases fully studied by me prior to 1942 reporting potentially inhibitory conditions during this period.

Perhaps the most valuable service that one may render is prevention of sterility by efficient care of abnormal conditions complicating pubescence and puberty. A contribution by Shorr¹ in 1941 and recently by Schonfeld² stressed the fact that delayed puberty and retarded development of secondary sexual characteristics resulting primarily from endocrine imbalance tend to correction by spontaneous adjustment. Nevertheless, gynecologists and urologists often encounter the sequelae of

earlier hormonal disturbances. These cases are too varied in character and complex in etiology to discuss in a general review. Such patients should not be dismissed with casual advice or the administration of a tonic but should be kept under supervision while every hygienic advantage is arranged. Specialized care will occasionally be required.

The frequency with which infertility, with or without functional and developmental defects, is met in patients giving a history of poor health, severe illness, and violation of hygiene during the adolescent years is impressive. Only brief discussion is possible although the subject may well merit a special contribution.

Cases of relative infertility with abnormal adolescent histories are seen among certain of our Jewish population and those of foreign parentage with suggestive frequency. At an early age these patients often undertake arduous work which occupies every hour not devoted to eager study. A report of industrial labor by day, and work in the family store at night is not uncommon. In others, long hours of day labor in addition to aggressive attendance at night school have shortened hours of rest and excluded relaxation. In brief, their childhood is spent in a less privileged environment and through a moral adolescence and following early marriage they strive for the better life against great obstacles. Sterility is not limited to any one economic group.

Gonadal deficiency, concomitant in many cases with sexual apathy, underdevelopment of the generative organs and menstrual anomalies has been encountered so often in those excessively devoted to competitive athletics from an early age that an etiological relationship seems evident. Impressive cases, selected from many, include four former football players of all-American calibre and the captain of a college water polo team who subsequently became athletic director. Two women with excellent physiques who began serious training in early adolescence, one for rowing and the other for international honors in tennis, were found to have infantile uteri, and another wife who started practice as a stage gymnast at thirteen developed oligomenorrhea, miscarriage when pregnant and now at twenty-nine is threatened with the menopause. It is appreciated that these findings may be coincidental and the final answer must come from those who are in position to keep scientific records of large numbers of adolescents.

Another group of women in whom hopeless sterility might have been prevented by prompt diagnosis and operation during adolescence

is composed of those with permanent pelvic adhesions resulting from appendicular abscesses or complications requiring drainage. We have records of a few women in whom pelvic abscess complicated mumps or the exanthemata and ruptured spontaneously before recognition. Some cases of male sterility might doubtless be avoided if patients with mumps were more cautiously managed to prevent orchitis. It is surprising how often the reproductive organs escape observation in the care of immature patients. One husband who applied for artificial impregnation holds a permanent grudge against his parents and the medical profession because, having had every economic advantage in youth, he nevertheless reached maturity and married without knowing he had double cryptorchidism.

Obesity, malnutrition and asthenia should be carefully treated during childhood for these conditions often keep children from normal play with their fellows and concentrate their attention upon books so that they may reach maturity as frail and rather neutral persons sexually. Their fertility is often low but they frequently marry pronounced sexual types.

CONTEMPORARY HISTORY

In addition to the usual gynecological and urological factors, the contemporary history should include circumstances incidental to modern living which tend to reduce physical vigor and which are reflected in some patients by impaired fecundity. Such items should include character and hours of work, fatigue and irritation associated therewith, recreation and manner of exercise, extent and type of vacations, psychological and physical strains when complicated by excessive fatigue, menstrual disturbances or temporary impotency. Finally, the patient's adjustment to marriage should be reviewed. From a group of thirteen couples, for the most part highly educated, who had been married from two to nine years and were referred as obscure problems, at least nine babies were obtained when special investigations revealed that the sexual union had not been fully consummated. The causative factor was revealed in another perplexing problem when the wife explained certain conflicting findings by the naive assertion that the husband was so vigorous sexually that he habitually ejaculated before penetration.

It would be presumptuous to discuss the physical examination before this audience except to urge that the status of the blood and the rate of

metabolism should be determined by clinical and laboratory tests because subnormal blood pressure, moderate degrees of secondary anemia and some depression of the metabolic rate often are concomitant with impaired fertility. Such findings are often elicited in persons of sedentary habits whose work entails continuous nervous exhaustion and excludes opportunity for outdoor exercise, relaxation and consideration for proper nutrition. I have come to recognize a certain type of woman of the slender, hyperfeminine kind who is devoted to her home and husband and is indifferent as to physical stamina. Frequently, there is a history of malnutrition and anemia during puberty, disturbances in development and in the establishment of menstruation. They commonly marry late in life and their sexual behavior is prompted by devotion rather than passion. Although never vigorous they rarely need to consult a physician until prompted by failure to conceive. The proper treatment of these patients involves rearrangement of their daily lives, physical training, balanced diet and therapy as indicated by the basic clinical findings. The indiscriminate administration of vitamins does not constitute such attention. The same rule applies to some men.

When the physical findings are normal in these cases of functional infertility it is probable that one is dealing with intrinsic glandular deficiency. Patients with indefinitely prolonged suspension of spermatogenesis and menstruation following nervous shock are included in this group. Daily vaginal smear studies have revealed no follicular influence in the very few cases observed in this group. Unfortunately, we are without any product directly stimulating spermatogenesis or oögenesis. In the opinion of myself and others thyroid preparations given in increasing dosage under repeated supervision constitute the most reliable adjunct to the general care of these patients. It may be well tolerated when indicated by clinical findings although the laboratory readings may be found in the low normal range. Many successful cases might be cited in which efficient hygienic and medical care, as previously outlined, constituted the chief or at least an important part of treatment. The result in cases of this type is necessarily long delayed. It should be repeated that the above statements are predicated upon the assumption that local organic lesions have been eliminated.

Many unusual cases might have been enumerated but they would not affect the theme of this paper which is that by directing the sexual education and hygiene of the adolescent and in recognizing impaired

physical or nervous vigor as a potential factor in relative infertility the internist may make an important contribution to the management of this problem.*

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* Lantern slides were used in the presentation of this paper.

LIBRARY NOTES

*A PLAN FOR HOSPITALIZATION INSURANCE DEVISED BY
PIARRON DE CHAMOUSSET, 1754*

GERTRUDE L. ANNAN

SINCE hospitalization insurance has only recently become available to the American public, it is astonishing to discover a practical plan devised in the eighteenth century which compares favorably with that in operation today. In view of the appalling conditions existing in contemporary hospitals, it must have seemed pure fantasy at the time of its publication. But the author of the anonymously printed *Plan d'une maison d'association*, [Paris, 1754], was no idle dreamer. Claude Humbert Piarron de Chamousset, 1717-1773, the son of a distinguished and wealthy family, dedicated his life to reforms in public welfare and worked passionately and zealously for their consummation.

His attention was drawn to foundlings, beggars, postal service and water supply. He proposed a registry for servants and workmen, and was instrumental in the founding of fire insurance companies. The poor were his "family," and anything that might help them stirred him to action. Not content with publishing his ideas and putting them before the authorities, he lavished his fortune upon them and turned his own home into a hospital where the indigent could receive the best of treatment.

Although his name is seldom mentioned in the history of medicine, his chief contribution was made in the care of the sick. His plan for hospitalization insurance did not materialize for lack of subscribers, but his determination to improve the frightful conditions in the Hôtel-Dieu brought them to the attention of the government. After the fire of 1772, which destroyed most of the hospital, legislation was enacted, decreeing that the new hospital be built according to plans which in a large measure followed those of Chamousset. Unfortunately controversies delayed

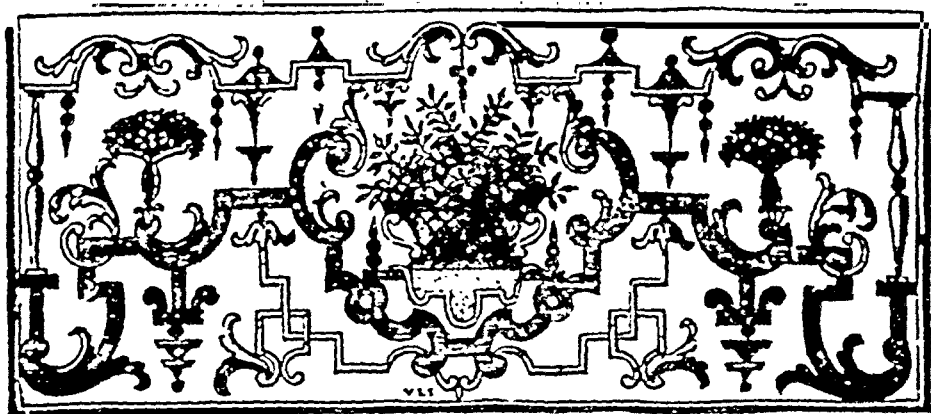
construction, and Chamousset did not live to see his ideas carried out. Marcel Fosseyeux in his *L'Hôtel-Dieu de Paris*, Paris, 1912, gives a brief account of his suggestions. Chamousset is said to have studied medicine, and he served for a time as Inspector of military hospitals, but his attempted reforms receiving no encouragement, he gave up that position.

In 1905 a work was published which brought Chamousset's name temporarily out of obscurity. F. Martin-Ginouvier's *Un philanthrope méconnu du XVIIIe siècle, Piarron de Chamousset*, contains a biography of Chamousset together with a reprinting of the *Plan*, Chamousset's *Additions*, which were also printed in 1754, an anonymous "Lettre critique," condemning the plan, Chamousset's reply, and several letters from prominent contemporaries on the subject. The author of the "Lettre critique" felt that the French were too indifferent to show enthusiasm about such a project. He also held the poor in low esteem and claimed that Chamousset's opinion of them was much too flattering. His estimate of the medical profession was not much higher.

Among the letters published by Martin-Ginouvier is one from a well known physician and anatomist, Antoine Petit. He wrote to Chamousset, July 20, 1770, "Your calculations are too high by half . . . nevertheless I think you would do well to reckon from those figures, exaggerated though they may be, because in making such plans it is wise to put the charges as high as possible, even a little above what is right, for the number of accidents is never small . . . I am sure that if, some fine morning, it should please Providence to show the poor their true interests . . . more than a fourth who might perish would be saved. Let your plan accomplish then what Providence, because of our sins, refuses to do. . . . Let the fire which consumes you continue to burn; the pleasure of doing good will repay you more than any other reward."

Unfortunately Providence did not one fine morning show the poor their true interests, and though Chamousset met with approval from the government, those his plan was designed to help did not respond. He did not cease to work in their interests until his death in 1773. His critic had not been wrong when he wrote that the poor would not be interested. His error was in not realizing that Chamousset was in advance of his times, and that the future would see the fulfillment of the vision of the "unknown philanthropist."

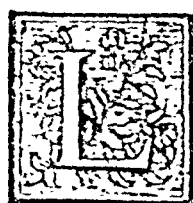
Examples of his writings are rare in this country. The Boston Pub-



PLAN

D'UNE MAISON D'ASSOCIATION,

*Dans laquelle au moyen d'une somme très-mo-
dique chaque Associé s'assurera dans l'état de
maladie toutes les sortes de secours qu'on peut
désirer.*



L'ETABLISSEMENT que nous proposons, nous a paru
avantageux aux Citoyens, & d'une exécution facile.
Nous allons en montrer le besoin, & en exposer le
Plan avec le plus de clarté & de simplicité qu'il nous
sera possible : afin que le Public qui en recueillera les
fruits, puisse juger de l'intérêt qu'il y doit prendre.

Les hommes sont la plus grande richesse d'un Etat, & la santé
est le bien le plus précieux des hommes. Mais ce n'est pas assez
qu'il ne leur manque rien pour la conserver lorsqu'ils en jouissent ;
un objet pour eux des plus importants, c'est de pouvoir, en cas de
maladie, compter sur tous les secours nécessaires pour la recouvrer,

Ces secours supposent trois choses principales, dont le concours
n'est pas moins essentiel que rare. De la dépense de la part des Ma-
lades, de l'intelligence dans ceux qui les traitent, du zèle dans
ceux qui les soignent. La privation de l'une de ces trois choses a des
suites fâcheuses, dont on n'est que trop instruit par l'expérience.

A

lic Library possesses a copy of his *Oeuvres complètes*, Paris, 1783, and the Army Medical Library owns his *Deux mémoires: le premier, sur la conservation des enfans . . . le second, sur les biens de l'hôpital S.-Jacques*, 1756, and *Lettres sur l'usage d'une nouvelle découverte de pâtes, de syrops et de tablettes d'orge*, Paris, 1772. The New York Academy of Medicine Library recently was able to purchase the little pamphlet from which the following translation was made. It is not possible to determine at present whether it is from the undated edition known to have been published in 1754 or the first part removed from a copy of the collection of the author's writings published in 1757 under the title *Vues d'un citoyen*.

PLAN OF A HOSPITAL ASSOCIATION

IN WHICH BY MEANS OF A VERY MODEST SUM EACH MEMBER WILL
BE ASSURED IN CASE OF SICKNESS OF ANY KIND OF

ASSISTANCE WHICH HE MAY DESIRE

[BY CLAUDE HUMBERT PIARRON DE CHAMOUSSET]

The establishment which we propose has seemed both advantageous to citizens and easy of accomplishment. We are going to show the need of it and describe the plan as clearly and simply as possible, so that the public who are to receive its benefits can determine what interest should be taken in it.

Men are the most valuable possession of a state, and their health is their most valuable possession. But it is not enough that they have the means of preserving it. An object of more importance to them is that in case of sickness they may count on all the aid necessary to their recovery.

This assistance presupposes three principal things in which cooperation is as essential as it is rare: the expense on the part of the patients, the intelligence of those who treat them, and the zeal with which they care for them. The lack of one of these three brings bad results which we know only too well by experience. Nevertheless, can even the rich flatter themselves that they can have all three? Can they have at their beck and call at every hour of the day or night able physicians, experienced surgeons, all waiting to administer or discontinue an appropriate remedy, which, according to circumstances, becomes from one moment to the next salutary or harmful? Can they always count on the accuracy and intelligence of those destined to make up prescriptions? Besides, do

they not fear the unenlightened zeal of a frightened family who through eagerness uses haste where it is necessary to delay, or who in mistaken sympathy defers treatment when speed is required? I make no mention of the dangers to which they are exposed when they are attended only by servants engaged by chance, or by those who dream only of the spoils.

There are asylums available to the destitute, and that is a resource useful to those to whom it is not humiliating to accept the free assistance which charity offers.

But between these two extremes is the class of the greatest number of citizens, who not being rich enough to procure sufficient aid at home or poor enough to be taken to an almshouse, languish and often perish miserably, victims of the propriety to which they are subjected by their class of society. Such are the industrious artisans, merchants whose trade is limited, and in general all those valuable men who live daily by the fruits of their labor, and who often for that reason have no recourse to treatment when a disease becomes incurable. The start of a disease exhausts all their resources; the more they deserve help, the less can they bring themselves to profit by the only resources that remain to them, and they find themselves in public asylums.

The air seems to them to be corrupted by the diseased and dying; they feel that the care is insufficient since there is no charge, and the continual spectacle of grief, agony and death in the room to which they have been conveyed, often in the bed where they are put, make them envisage in hospitals dangers more frightening than those to which their misery exposes them at home.

The literary men who assemble at Paris from all parts of the kingdom; the military who come to solicit remuneration for their services; litigants forced to make long stays in order to uphold their rights, and that crowd of strangers which curiosity brings here, are in the most dangerous situation as soon as they fall sick. Isolated and abandoned to the discretion of unknown people who surround them, must they await the care of those for the most part greedy and selfish? How few men can then be assured of having all the necessary aid when they are ill? And others, can they not be touched by the situation of their fellow citizens? Is it not humanity for them to at least interest themselves in the preservation of their servants? Can they persuade themselves to abandon the unfortunates who have lost their health in their service? Is it always

possible to treat them at home; and when they can do so, do their affairs permit them to provide the proper care? Are they not obliged to depend upon other servants, that is to say, on men whom hardness or jealousy nearly always renders negligent?

It is then of interest to all citizens to form an establishment which furnishes all the necessary aid to the sick, and which guards against all the inconveniences of which we are about to speak. For this it is necessary 1°. that the rich be received in a manner which leaves nothing to be desired, even to their niceties; 2°. that the treatment in sickness be absolutely the same both for them and for those less fortunate; 3°. that the expense be suited to the means of those in the hardest circumstances; 4°. finally that propriety hinders no one from profiting from the aid offered them. Such is the principal object of this establishment which we propose to the public, and it will be executed by a free association which will continue only as each member finds it to his advantage, and by which one may acquire by paying each month a most modest sum the right to procure all the aid one might need in case of illness either at home or in a hospital, of which one becomes co-proprietor by joining this association.

This project can be fulfilled wholly to this extent or a trial establishment can be attempted at first, whose success could lead to the execution of the greater plan. In the first case a spacious building would be constructed, divided into appropriate and commodious rooms and composed of several corps of houses entirely separate and laid out according to the different conditions of the people for whom they are destined, some for men and others for women. In each the service will be only for people of the same sex.

A complete pharmacy will be established there, provided with excellent drugs and managed by most intelligent men. Physicians and surgeons in chief will be assembled, selected with all possible care, who will be attracted equally by the honor of filling such positions and by the salaries attached to them. Other physicians and surgeons of sufficient number and living also at the hospital will work assiduously under the eyes of their chiefs, healing the sick, some prescribing, others dressing the wounds of those who have undergone operations. A fixed number of young physicians will be received, lodged and fed, for a modest fee, who doubtless will be eager to train there and who will at the same time be of great help at the bedside of the sick, reporting to the phy-

sicians the effects of their prescriptions and an infinity of enlightening observations to render the treatment more certain.

Two of the most celebrated physicians of Paris will come regularly every day to consult with those who live in the establishment and decide together the puzzling cases which demand mature deliberation. If it happens that a patient has confidence in a physician or surgeon who is not connected with the hospital, he will be free to associate himself at his expense with the other physicians and surgeons of the hospital.

In order to prevent mistakes and to keep the condition of the patients always under the eyes of the physician as well as the symptoms which he has noticed, all prescriptions will be written, also the regimen, and placed at the patients' bedsides. Furthermore, it will be a new means of study and observation for young physicians, not counting the fact that this way of writing prescriptions will make the physicians more attentive in composing them.*

Surgery will be cultivated with no less care, and there will be added to the number of surgeons, aides and boys admitted and boarded in the hospital, other pupils paying also a very modest sum for their food and lodging. These will be trained under the eyes of the masters and will be inspired by the hope and desire of winning in the competition, the only way by which any of the positions in the hospital may be obtained. Add to that vigilant care and surveillance, a scrupulous choice of the proper foods, and every attention to cleanliness to prevent disgust and to avoid unpleasant atmosphere. Such are the principal precautions to be taken for the treatment of patients and the care of diseases in general.

It may be seen that in this hospital the rich will receive prompt and continual aid which they cannot expect to find at home, no matter how wealthy they are, and it will be given to all with the same zeal. This establishment will contribute to the relief of families and the preservation of citizens.

There will necessarily result from the policy of this hospital two general advantages which should forcibly strike every man who loves his fellow man and even him who loves only himself.

The first is the attention so necessary in the momentous changes that occur in the course of a disease. How many times has it happened that Nature has spoken and there has been no one to hear? And how many

* Each month a brief statement will be published showing the treatment and remedies which have been most successful in current diseases.

times has this inconvenience alone, from which even the rich cannot always shield themselves, been fatal to the patient? If skill cannot be blamed for this, is it not the same in ordinary practice where it is impossible or at least very difficult to prevent it? The second is even an improvement in the art of healing. It will be agreed that histories of cases made after continuous observations, that is to say, from moment to moment, from the commencement up to the happy or unhappy termination, will be necessarily more detailed, more exact, and consequently more calculated to advance medicine and surgery, than those which can be published by physicians who see so many patients that they are reputed to be very capable, and who could never describe all the cases they have treated, just as if they had observed only one or two.

The hospital will be governed by an administrative body, sufficiently large, elected every three years, but no one can be elected except members.

Intelligence, zeal and integrity will be the only qualifications required for admission, and probably for appearance before the government of a hospital where one will find no other advantage than that of devotion to the relief of humanity and to the service of fellow citizens. Paris includes a great number of inhabitants enlightened, rich and charitable, who would be honored with a choice which bears witness to their honesty and zeal for the public good.

None will have the right to the assistance of this hospital except those who have been admitted to membership, and in order to allow for different conditions and means, there will be established five classes of members who will pay more or less, not for treatment of their diseases (for all classes will receive the same care), but for optional accommodations which vary according to conditions and which are necessary only to those who habitually enjoy them.

Each member of the first class will occupy a complete apartment and will be furnished and served in a manner suitable to his way of life. Those of the second class will each have a separate room; those of the third will be in rooms containing two or three beds; the fourth will be assigned to halls with a dozen beds; and the fifth in halls with thirty beds in which the patients will never be side by side, as each of the beds will be enclosed by a partition which will form a little room.

Thus every member, released from anxiety concerning the treatment of diseases which may attack him, surgical operations which he may

require, and even support during those times when his work is suspended, would have nothing to worry about except the recovery of his health.

The cost of membership will be enough for the establishment of the large scale plan which we propose, and yet will not exceed the means of the poorest citizens. This has been studied for a long time and is based upon very accurate computations. It can even be hoped that once the establishment is started, conditions for members can be made still more favorable, since evaluations have been set high so that the promises made to the public can surely be carried out in any event.

Here is the table of the different prices which members will pay according to their age and class. You will notice that only those between fifteen and sixty may join. But the membership fee never changes for those who are punctual about continuing their membership; it remains just what it was when they started, and their membership has no other termination than that of their life. Heads of families should receive an advantage over others, that of paying the price fixed for the class between 15 and 35 years for each member of the family rather than paying per person according to age.

[The abbreviations in the following table refer to *sol*, half penny, and *livre*, franc.]

| Members will pay by month— | Rooms with 30 beds | Rooms with 12 beds | Rooms with 3 beds | Rooms with 1 bed | Apart- ments |
|-----------------------------|--------------------------|--------------------------|-------------------------|------------------------|-----------------|
| From 15 to 35 years of age— | 25s. | 30s. | 40s. | 3 l. | 5 l. |
| From 35 to 40 “ “ “ | 26 | 32 | 43 | 3 45. | 5 8s. |
| From 40 to 45 “ “ “ | 27 | 34 | 46 | 3 8 | 5 16 |
| From 45 to 50 “ “ “ | 28 | 36 | 49 | 3 12 | 6 4 |
| From 50 to 55 “ “ “ | 29 | 38 | 52 | 3 16 | 6 12 |
| From 55 to 60 “ “ “ | 30 | 40 | 55 | 4 | 7 |

Members will pay by month as much when they are well as when they are sick. This has seemed to be the most convenient way, either because it is the easiest way to make payments, or so that they will not get so far in advance in their payments to the establishment that in case of emergency they will have to ask for a refund.

Therefore, they will carry their quota every month to one of the notaries named below, where it will remain on deposit until the end of the month for which it was paid; those who will find it more con-

venient to pay for a year in advance will be free to put the entire sum in the hands of the notary who will month by month pass it on. They will receive, on paying the first month's installment, a card of membership formulated to prevent any ambiguity or deceit. On this card, accompanied by the monthly receipts (if several months have elapsed since admission) they will be admitted when they are ill to occupy their lodgings in the hospital.

Let us propose some conditions which prudence suggests and which fairness should make agreeable. That is 1°. that there be an interval of a month between the date of membership and the date of admittance to the hospital, for the first time only; 2°. that in case anyone allows his membership to lapse and then takes it up again, he must pay double the cost the first month only; 3°. that in such a case the monthly interval should be imposed as if it were an entirely new membership. The cost of the membership card is so modest and other penalties for negligence so just and so light that no one ought to object. If the cards were not annulled for non-payment, it would be impossible to keep track either of members or vacancies.

Bodies or groups which would like to join, will pay every month into whatever class they wish for masters, apprentices, workmen and even their servants, five *sols* per head less than private individuals, and then the agents or deputies elected by each body will receive the fees of the members of the group and they will send immediately to the treasurer of the hospital the sums which they have received, and for mutual satisfaction, one of these agents will each year be admitted to the board of administration.

There will be separated and isolated places for contagious diseases. And for pregnant women the only qualification will be that they have been members for at least nine months. Preference will be given to those whose husbands are members. The only diseases excluded by the association are venereal diseases and incurable diseases,* but in the case of exclusion for incurable diseases, and those judged as such by a consultation of physicians, that member will be repaid all the money he has paid in to the association during that period, even though he has already profited by assistance from the hospital in preceding illnesses.

* It is obviously impossible at the beginning of such an establishment to take care of incurable cases, since one incurable patient would deprive several citizens of aid which they could successively receive; thus we are obliged to exclude those cases until the eagerness of the public for this present association induces us to present to it a project we are considering for a hospital where such cases may be received.

How much expense will not this assistance save them? For ordinarily the fact that a disease is incurable is not immediately apparent. It is only after several attacks that this sad state of affairs can be determined. It is somewhat alleviated in the cases of those unfortunates to whom restitution is made for all that which they have spent, little by little, from the day they joined the association up to the moment that the incurability of the disease is verified.

Every disease, other than those above-mentioned, which is accompanied by fever or which necessitates an operation, will give the member so attacked the right of being transported to the hospital and of occupying a bed, a room or an apartment, according to the class in which he has been registered; and he will never under any pretext whatsoever, have to leave the hospital until he is completely cured, or declared incurable; nor can admittance to the hospital be refused to any members recovered from an illness who suffers a relapse, whether his relapses be lengthy or often, or whether or not they are his own fault.

Out of town patients, or others, will be given an account of their personal effects which they have deposited at the hospital, and these will be entered on a register, so that they can be returned either to the patients themselves when they are cured or to their representatives in case they are not.

Whenever a member is ill in the hospital he will be visited, treated, fed, provided with medicine, observed, kept warm and clean, etc. with the greatest care until he is entirely well; he will enjoy all the special accommodations of his class without either preference or exclusion, whoever he may be. If he needs a surgical operation, that will be done after a consultation of physicians and surgeons who have treated him, without his being asked for any payment beyond his membership fee which he paid while in perfect health, for whatever operation or medical treatment necessary, no matter how long his illness lasts.

In an unusual instance, such as an epidemic, which suddenly increases the number of patients, so that the hospital cannot accommodate all the members who ask for admittance, the association will be obliged to furnish them at home with the same assistance, physicians, surgeons, medicines, broths and other nourishment. But in every other circumstance, if the ill members prefer to stay at home, the association will provide only the physicians, surgeons and medicines; food will be at

their own expense, except in certain cases. The administration which will be animated only by consideration of public welfare, judges only whether or not it is proper to leave a patient to the care of a family in which his presence seems to be necessary, whether for his own consolation or for the conduct of business which must be directed from his bedside, or for the support of his family.

In urgent cases, such as when a patient, not needing to occupy a bed in the hospital, is not in a condition to be carried there in order to consult physicians, the necessary remedies will be provisionally furnished by the hospital. In order to fulfill this promise, the hospital will recompense physicians and surgeons in different parts of Paris.

Those living in the provinces will know the advantage of enjoying the privileges of membership in the unhappy circumstances which demand aid not to be found outside the capital and which they are so often obliged to seek there, for they will procure the advice of the most celebrated physicians and the skill of the ablest surgeons in the same hospital where they will be admitted and treated for diseases requiring surgery, and outside of the hospital they will be provided with all the medical, surgical and pharmaceutical assistance necessary in chronic diseases. The only requirement, to which they should not object, is that applied indiscriminately to all, that they should be in perfect health when they ask for membership. Since distance will deter out of town patients from receiving any aid from the hospital in ordinary diseases, they will pay only half of the fee for ordinary members, but since the establishment can accommodate at the start only a certain number of those interested, those will be selected who were the first to apply to the notaries. The latter will supply their dates of application.

In regard to those who may have fallen sick without having joined the association, if they wish to be admitted to the hospital, they can only be received as day patients, and they will pay by day and in advance the prices listed below. But since they have no right to the hospital, only as many will be received into the classes they have chosen, as there are vacancies available not required by members.

So much confidence may be placed in the efficacy of the care which all will receive, that it is proposed that the day patients, attacked with acute diseases who have not yet been treated, and those who need surgical operations, will be admitted to the hospital by giving bond for the duration of their stay on the condition that the charge will be one

fourth over and above the ordinary price if they are cured and nothing at all if they die.

| | |
|--|--------|
| Day patients of the first class will pay by day | 7 l. |
| Day patients of the second class will pay by day | 5 |
| Day patients of the third class will pay by day | 3 10s. |
| Day patients of the fourth class will pay by day | 2 10 |
| Day patients of the fifth class will pay by day | 2 |

Eventually when the establishment has won fame and the firm foundation we have reason to hope for it, and its benefits, different ways will be found of procuring the right to receive the assistance of the association. There will be life-subscriptions, subscriptions covering certain periods of time; there will be fees for those who with a small addition to their quota may acquire the right of indefinite stay in the case of an incurable disease or senility; thus the association will become a resource for those excluded from the original association.

No citizen of whatever condition possible can disapprove of such an establishment, for the description we have just given of it shows that its basis is decency. Since the establishment properly belongs to the body of members, there is no charity in the assistance which they receive; if the need arises that they are obliged to seek refuge in the hospital they will be as if at home; the care that they receive will be as a debt for which they could demand payment. The funds of the establishment will be theirs. No gifts, legacies, endowments, will be accepted, nor can anyone give anything beyond his quota. Any payments received by those who care for the patients, no matter what the right or pretext, will be treated as extortion; for since that becomes the germ of a dangerous corruption, members must have no part in it. And so their rights can never suffer the least moderation, nor their delicacy the least anxiety, the hospital will accept nothing whatever beyond the protection of the King who will be asked to confirm it by letters patent as soon as experience shows us better ways of organizing the establishment, so that royal authority can render them irrevocable and inalterable.

The establishment having no funds other than the quotas of the members, it would not be discreditable to receive assistance already paid for. No one could pity anyone else, since each will have his own interest in it. All establish the funds together, for no one can be assured of continual health, and if those who are fortunate enough not to be com-

pelled to seek recourse there furnish the association with more than the association renders to them, they at least enjoy the benefit of knowing there is such an asylum for them whenever it becomes necessary to take advantage of it; and by that they are exempt from anxiety. If when I am well, I pay a modest sum to my association for someone else who is suffering, then the same thing is done for me when I am sick. It is a general law of humanity put into execution in a prudent and deliberate manner. It is a bond of civilized society extended to a circumstance still more necessary than all those provided up to now.

In a word, this association, as in all those which it is an honor to join, is a community of funds established for the needs of all members. Can there be any dishonor in enjoying advantages one has procured for himself?

This establishment is not wholly a novelty; it has been carried out in part in Lyons, Chaalons sur Saonne, Beaune, Besançon, etc. But with less need because of the nature of the places and with less propriety because of the joining of these establishments with hospitals. That has not prevented people of the highest quality from going there to enjoy assistance which is more continual, more certain and more united than their wealth could assure them at home.

It is evident that an enterprise of this importance cannot begin its care without those to whom Providence has given wealth accompanied by zeal for public welfare; and we are glad to announce that some understanding souls have been found who are happy to accord their protection to our project and are ready to contribute the necessary sums for its execution. The question is, should the first foundations be laid of an establishment whose success depends entirely on public approval and the number of subscribers? The sums that equally well meaning people could offer us would only be accepted as a loan. A condition, voluntarily imposed, is to determine both the use of their funds and the time when they can expect to be repaid.

When we are assured of buildings to accommodate the sick and we know we have a sufficient number of subscribers, then the doors will be opened and every individual will be welcomed to give advice on the arrangement of the hospital of which he can become one of the proprietors by joining the association.

The establishment, whether in the beginning or after its complete execution, will belong to the members and the members alone, so that

if it fails because of some unforeseen circumstance, the sums coming from its effects and its funds will be returned to the members according to the proportion of the amount contributed, counting from the time they joined the association.

The administration in the name of the members and under the eyes of the magistrates will enjoy the right of acquiring or transferring property according to the needs of the case. Thus the savings made on the sums paid by each member in favorable years when there has been little sickness, will be allotted either to attain promptly the execution of our more ambitious plan or to aid resources in less fortunate years, making such transfers according to our needs. For it is not a question of establishing a wealthy hospital, but of making it capable of completely fulfilling the mutual promises that the members of the association have contracted to relieve the expenses of all those among them who fall sick.

The members being joint proprietors of the funds of the establishment, they should be informed of its activities. Also the administration should be obliged to render every year to the public an exact account of the progress of the association, of its expenses and its accomplishments. The names of the members in each classification should be printed at the beginning of January, as well as the number of patients admitted to the hospital during the year, the number of those who recovered their health, the amount it cost to take care of them, and the other expenses of the establishment; and finally what funds remain in the coffers of the association. Such a practice will be the foundation of the confidence of the public.

They will be astonished at the advantages we flatter ourselves can be procured by this establishment. But if one reflects on what we reported at the beginning of this memoir, where we explained how few citizens can be assured of all the necessary care in case of illness, one would realize how large the number of members ought to be, and the money they provide could scarcely fail to exceed the expenses of the establishment.

For we know by observations of physicians that with a given number of men every year there are so many well, so many sick. The same observations also furnish the means of making a general estimate of the length of illnesses and the expenses they entail. Thus the possibility of the establishment we propose depends upon suppositions based upon the proportion of members that experience shows are destined to be ill and

the amount of money necessary for those who take care of them.

There are establishments which, though useful at the start, become a burden because of abuses which have crept in. This one, by its constitution, is such that since it can subsist only by the interest which the public takes in it, will necessarily fail whenever it ceases to be of advantage to its members; wholly voluntary, it cannot be a burden to anyone; and as it adds decent surroundings to modest expense, it will be accessible to all classes of citizens.

As the care to be found there is not extended further than for actual need, it cannot support idleness. Its efficacy will shorten the duration of the diseases and even prevent them from becoming more serious, because one will not have to wait for an emergency before having recourse to the proper remedies, but on the contrary, be cared for from the moment he feels ill. Thus services owed to the country will not be interrupted for such a long period. One will no longer see the families of artisans ruined by the length and excessive expense of illnesses or citizens a burden to their government when they should be its mainstay.

Those who approve of the project and would like to join the association are asked to subscribe at the notaries listed below, leaving a note signed by them in which they have indicated the number of memberships they need and the classification they have selected. The notaries will not charge for depositing these notes.

Although this kind of subscription is not obligatory, those sponsoring the association will have to rely upon the number of such subscribers in hastening the execution of their plans. The first thousand subscribers will be regarded as founders and will have that title bestowed upon them for more than ten years.

In regard to fees, the members will not begin to pay until the hospital is ready to receive them. Membership tickets will be distributed which will serve as certificates for admission. The establishment will at first have to be limited to a certain number. It is only fair that the first to join will be accepted, the others will have to wait until the establishment is larger.

It remains for us only to ask enlightened people, eager for public welfare, and animated by the same sentiments as those who suggested this project, to examine this plan carefully, and to communicate to us, either through the notaries or by papers appearing in periodical literature, useful observations on the project in general or in detail.

RECENT ACCESSIONS TO THE LIBRARY

"Possession does not imply approval"

- Armstrong, D. B. *What to do till the doctor comes*. N. Y., Simon, 1943, 354 p.
- Ashley-Montagu, M. F. *Edward Tyson, 1650-1708, and the rise of human and comparative anatomy in England*, Phil., American Philosophical Society, 1943, 488 p.
- Association for Research in Nervous and Mental Disease. *Pain*. Balt., Williams, 1943, 468 p.
- Association for Research in Nervous and Mental Disease. *The role of nutritional deficiency in nervous and mental disease*. Balt., Williams, 1943, 215 p.
- Blacker, C. P. *Notes for the R.M.O. of an infantry unit*. London, Milford, 1943, 77p.
- Bloor, W. R. *Biochemistry of the fatty acids*. N. Y., Reinhold, 1943, 387 p.
- Clendening, L. & Hashinger, E. H. *Methods of treatment*. 8. ed. St. Louis, Mosby, 1943, 1033 p.
- Conference on Traumatic War Neuroses in Merchant Seamen, New York, 1943. *Proceedings*. [N.Y., United Seamen's Service, 1943], 163 p.
- Davison, W. C. *The complete pediatrician*. 4. ed. Durham, Duke Univ. Press, 1943, 256 sections.
- De Kruif, P. H. *Kaiser wakes the doctors*. N. Y., Harcourt [1943], 158 p.
- Eliason, E. L. *Practical bandaging*. 6. ed. Phil., Lippincott, [1943], 128 p.
- Garrison, F. H. *A medical bibliography*, revised by L. T. Morton. London, Grafton, 1943, 412 p.
- Geckeler, E. O. *Fractures and dislocations*. 3. ed. Balt., Williams, 1943, 361 p.
- Haagen-sen, C. D. & Lloyd, W. E. B. *A hundred years of medicine*. N. Y., Sheridan House, [1943], 443 p.
- Kazis, H. *Planning and treatment for bite raising*. Brooklyn, Dental Items of Interest Pub. Co., 1943, 538 p.
- Lastres Quiñones, J. B. *Vida y obras del Dr. Miguel Tafur*. Lima, [Imprenta Americana], 1943, 126 p.
- Mira y López, E. *Psychiatry in war*. N. Y., Norton, [1943], 206 p.
- Molecular films, the cyclotron & the new biology; essays by H. S. Taylor, E. O. Lawrence & I. Langmuir*. New Brunswick, Rutgers Univ. Press, 1942, 95 p.
- Montgomery, D. W. *Collected writings, 1859-1941*. San Francisco, 1943, 2 v.
- Research Council on Problems of Alcohol. Scientific Committee. *Alcohol addiction and chronic alcoholism*. New Haven, Yale Univ. Press, 1942, 336 p.
- Ruiz Rodriguez, J. M. *La schistosomiasis mansoni en Venezuela*. Caracas, Lit. del Comercio, 1943, 224 p.
- Sante, L. R. *Manual of roentgenological technique*. 10. ed. Ann Arbor, Edwards, 1943, 351 p.
- Selye, H. *Encyclopedia of endocrinology. Section I: Classified index of the steroid hormones and related compounds*. Montreal, Franks, [1943], 4 v.
- Stern, K. & Willheim, R. *The biochemistry of malignant tumors*. Brooklyn, Reference Press, 1943, 951 p.
- Thorek, M. *A surgeon's world; an autobiography*. Phil., Lippincott, [1943], 410 p.
- Thorek, M. *Surgical errors and safeguards*. 4. ed. Phil., Lippincott, [1943], 1085 p.
- Toxicology and hygiene of industrial solvents*, edited by K. B. Lehmann and F. Flury. Balt., Williams, 1943, 378 p.
- Winter, L. *A textbook of exodontia*. 5. ed. St. Louis, Mosby, 1943, 576 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

DECEMBER 2—*The New York Academy of Medicine*. Executive session—a] Reading of the minutes. ¶ Papers of the evening, Diagnosis and treatment of painful diseases of the spine—a] Differential diagnosis and treatment, including non-surgical therapy, of conditions causing low back pain, Ralph K. Ghormley, Professor of Orthopedic Surgery, The May Foundation, Graduate School, University of Minnesota; b] Diagnosis of prolapsed nucleus pulposus; indications for surgical therapy, Roy Glenwood Spurling, Lt. Col., M.C., A.U.S. Chief of Neurosurgical Section, Walter Reed General Hospital. ¶ Report on Election of Academy Officers.

DECEMBER 16—*The Harvey Society in affiliation with The New York Academy of Medicine*. The Third Harvey Lecture, "Nutrition of the Single Cell; It's Applications in Medical Bacteriology," J. Howard Mueller, Professor of Bacteriology and Immunology, Harvard Medical School. This lecture takes the place of the second Stated Meeting of the Academy for December.

SECTION MEETINGS

DECEMBER 3—*Section of Surgery*. Reading of the minutes. ¶ Presentation of cases—a] A case of diverticulitis, Lester Breidenbach, Bellevue Hospital; b] Two cases of diverticulitis of the right colon, John C. A. Gerster, Lenox Hill Hospital; c] 1. A case of diverticulitis treated by colostomy; 2. A case of diverticulitis with urinary fistula, William C. White, Roosevelt Hospital. ¶ Paper of the evening, Diverticulitis of the large bowel, John H. Garlock, Marcy Sussman (by invitation). ¶ General discussion. ¶ Executive session.

DECEMBER 7—*Section of Dermatology and*

Syphilology. Presentation of cases—a] From New York University, College of Medicine; b] Miscellaneous cases. ¶ General discussion. ¶ Reading of the minutes. ¶ Executive session.

DECEMBER 9—*Joint Meeting Section of Pediatrics and New York Roentgen Society*. Papers of the evening—a] Experiences with surgery of the patent ductus arteriosus, Robert E. Gross, Boston (by invitation). Discussion—George H. Humphreys (by invitation); b] Roentgenological appearances in fifty confirmed cases of patent ductus arteriosus, Merrill C. Sosman, Boston. Discussion—Marcy Lee Sussman; c] Changes in the circulation resulting from patent ductus arteriosus, C. Sidney Burwell, Boston (by invitation). Discussion—Dickinson W. Richards. ¶ General discussion. ¶ Executive session.

DECEMBER 14—*Joint Meeting Section of Neurology and Psychiatry and the New York Neurological Society*. Papers of the evening—a] What type of soldier succeeds, Colonel William C. Porter (by invitation). Discussion—Lieutenant Colonel Douglas A. Thom, Lawrence K. Kubie; b] Some psychosomatic and therapeutic aspects of war neuroses, Paul Hoch (by invitation); c] Experiments in the rehabilitation of discharged service men, Thomas A. C. Rennie. Discussion—J. H. W. vanOphuijsen, Richard Brickner. ¶ General discussion. ¶ Executive session.

DECEMBER 15—*Section of Genito-Urinary Surgery*. Reading of the minutes. ¶ Papers of the evening by Residents in Urology (by invitation)—a] Two-year results in prostatic carcinoma under androgen control, Thomas J. Sullivan, Squier Urological Clinic, Presbyterian Hospital; b] Treatment of renal obstruction from sulfadiazine, Ole Jansen and Charles L. Fox, Squier Urological Clinic, Presbyterian Hospital; c] A re-

markable cure by the use of penicillin, Albert Verges-Flaque, Brady Clinic, New York Hospital; d] Lymphangioma of epididymis, J. Scott Gardner, New York Hospital; e] Effect of certain biologically important salts on activity of sulfonamides, Bernard Pinek, New York Post-Graduate Hospital; f] Blood phenol in azotemic states—a clinical and laboratory study, Philip R. Roen, New York Post-Graduate Hospital. ¶ General discussion. ¶ Executive session.

DECEMBER 15—*Section of Otolaryngology.*

Reading of the minutes. ¶ Case presentation. Recovery of a case of cavernous sinus thrombosis in which sulfathiazole was used. (*Patient presented*), Arthur J. Herzig. ¶ Papers of the evening—a] The management of otolaryngic casualties as seen at Halloran General Hospital, Kenneth M. Kahn, Lt. Col., M.C. (by invitation). Discussion Samuel J. Kopetzky; b] Masking effects of sulfonamides on otogenous infections, Lester L. Coleman (by invitation). Discussion, Jacob L. Maybaum, Daniel S. Cuning (by invitation). ¶ General discussion.

DECEMBER 17—*Section of Orthopedic Surgery.*

Reading of the minutes. ¶ Presentation of a case. *From the Orthopedic Service of the Kings County Hospital.* Tuberculosis of the cervical spine with quadriplegia, treated by laminectomy and subsequent spine fusion, Charles Vitale (by invitation). ¶ Papers of the evening—a] The effects of violence on ankylosed extremities, Sigmund Epstein; b] Blastomycosis with osseous complications, Paul C. Colonna, Thomas Gucker, 3rd (by invitation); c] Posterior approach to the femur, David M. Bosworth. ¶ General discussion. ¶ Executive session.

DECEMBER 20—*Section of Ophthalmology.*

Instruction Hour 7:00 o'clock. Intraocular foreign bodies—Dixon method of localization, Irving Schwartz. ¶ Reading reports—a] Extraction of foreign body in cataractous lens; b] Injury to the ciliary body without iridocyclitis; c] Detachment of retina resulting from traction by intraocular foreign body, A.

Russell Sherman. d] Transscleral removal of intraocular foreign body localized with the Berman locator, Henry Minsky. ¶ Papers of the evening—a] Concerning the management of industrial eye injuries, Elbert S. Sherman; b] The management of corneal lacerations, Albert C. Snell, Jr., Wilmer Institute (by invitation); c] The contact lens method of foreign body localization, Raymond L. Preiffer; d] Desirable revisions in New York State compensation Laws, Albert C. Snell, Sr. (by invitation).

DECEMBER 21—*Section of Medicine.*

Reading of the minutes. ¶ Papers of the evening—a] Progress in the sulfonamide prophylaxis of acute infections, Wheelan D. Sutliff, Assistant Director for Clinical Investigation Division, Bureau of Laboratories, N. Y. City Health Department (by invitation). Discussion, David P. Barr; b] Sulfadiazine in the treatment of meningococcic meningitis and meningococcemia, Emanuel Applebaum, Assistant Director of Bureau of Laboratories, N. Y. City Health Department. Discussion, David D. Rutstein (by invitation).

DECEMBER 28—*Section of Obstetrics and Gynecology.*

Executive session. ¶ Reading of minutes. ¶ Case reports—a] Two cases of paralytic ileus postpartum, A. C. Posner (by invitation), J. I. Kushner; b] Case of lung abscess with sepsis. Recovery (lantern slides), M. Rosensohn; c] Case of Naegele's pelvis due to lack of development of femur. Spontaneous delivery (lantern slides), P. B. Wahrsinger (by invitation); d] Pregnancy at term in prolapsed uterus with prolapse of cord (lantern slides), I. Kibel (by invitation). ¶ Papers of the evening—a] X-ray pelvimetry based on 3,500 cases, William Snow; b] Cesarean section at the Bronx Hospital, P. B. Wahrsinger (by invitation), J. I. Kushner. ¶ General discussion, J. W. Hinton, Harry Wesler, Harry Aranow, H. C. Williamson, S. W. Boorstein.

AFFILIATED SOCIETIES

DECEMBER 9—*New York Roentgen Society*
—See program of Joint Meeting with
the Section of Pediatrics.

DECEMBER 15—*Society for Experimental
Biology and Medicine, The New York
Section*. Papers of the evening—*a*] A
microbiological method for the deter-
mination of tryptophane, R. D. Greene
(by invitation), A. Black (by invita-
tion), (Introduced by H. B. van Dyke);
b] Primary carcinoma of the liver in
mice following the subcutaneous injec-
tion of methylcholanthrene, L. C.
Strong; *c*] Effect of thiourea on thyroid
activity, A. S. Gordon (by invitation);
E. D. Goldsmith (by invitation); H. A.
Charipper; *d*] Variations in behavior
of buffy coat cultures from individuals
of different constitutional types, G.
Draper, H. Ramsey (by invitation); *e*] *Recording of blood pressures in the
right auricle and ventricle in normal
man and in cardiac patients, A. Cour-
nand (by invitation); H. D. Lauson (by
invitation); R. A. Bloomfield (by in-
vitation); E. S. Breed (by invitation);*

*E. de F. Baldwin (by invitation), (In-
troduced by H. W. Smith); f*] *Observa-
tions on acquired, non-specific resist-
ance to equine encephalomyelitis virus*
R. W. Schlesinger (by invitation); P.
*K. Olitsky, I. M. Morgan (by invita-
tion); g*] *Electron microscopy of the
virus of lymphocytic choriomeningitis*
adsorbed on glass surfaces, G. Shwartz-
man.

DECEMBER 23—*The New York Pathological
Society*. Presentation of cases—*a*] *Re-
peated and fatal hemorrhage from a
small angiomatous polyp in the ileum,*
Silik H. Polayes, Thomas F. Nevins (by
invitation); b] *Actinomyces bacteremia*
in a case simulating subacute bacterial
endocarditis clinically and anatomically,
Louis Lichtenstein, John E. Blair (by
invitation). ¶ Papers of the evening—
Poisoning from pentachlor-naphthalines
—a] *Clinical and chemical findings,*
Lawrence H. Cotter; b] *Gross anatomic*
findings, Milton Helpert; c] *Histologic*
findings and comparison of these with
those in cases of poisoning from organic
arsenicals, Edith Sproul (by invitation).
¶ Executive session.

CLINICAL RESEARCH MEETING TO BE HELD BY THE NEW YORK ACADEMY OF MEDICINE

The New York Academy of Medicine will hold a meeting in the first week of April to provide a forum in which research workers of New York City and vicinity may present results of original research in clinical medicine.

This meeting is being arranged by the Committee on Medical Education of the Academy in view of the dearth of meetings of national medical societies before which research work has usually been presented.

Presentation will be limited to twelve minutes. A brief period of free discussion will follow each presentation. The publication of presentations is not a necessary condition but the Academy plans to publish in the BULLETIN abstracts of presentations, if

the author so desires. The fact that material has in substance or in part been presented elsewhere will not be regarded as a bar to presentation, provided that the work represents recent research.

The Committee extends an invitation to all research workers of Greater New York and neighboring cities within a radius of one hundred miles to submit an abstract, not to exceed two hundred words in length, of proposed presentation to the Secretary of the Committee on Medical Education of the Academy not later than March 1, 1944. A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation.

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BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE



MARCH 1944

PRESIDENTIAL ADDRESS*

ARTHUR FREEBORN CHACE

President, The New York Academy of Medicine

THE ACADEMY IN THE VANGUARD



ONE year ago tonight, in assuming the office of President, I spoke to you on the theme, *The Academy Meets The Challenge Of The Future*. This evening I come to you to give an account of our stewardship.

The challenge of the future, I said a year ago, was evident to everyone. Wanting was the knowledge of how best to meet it. In that connection I promised that the Academy would "institute in the immediate future . . . careful and thorough-going studies of the trends and the indicated future developments in medicine and in communal and public health" and furthermore that the Academy would "scrutinize carefully the proposals and plans for the post-war world that are formulated by responsible and authoritative agencies in order that we may be fully informed and in a position to contribute effectively such services as we may be ultimately called on to render."

This promise, I am happy to inform you, has been fulfilled.

Early in 1943, there was formed, under the able leadership of Dr. Malcolm Goodridge, a Committee on Medicine and the Changing Order. Fourteen Fellows of The New York Academy of Medicine, eminent

* Read at the Annual Meeting of The New York Academy of Medicine, January 6, 1944.

for their knowledge and service in the social and economic fields of medicine, were chosen to serve on this Committee. To these were later added thirty-one committee members representing the leaders of thought in the fields of labor, law, social work, nursing, medical education, dentistry and public health.

The Committee is pursuing its work with unremitting energy and devotion. It meets weekly, bringing to its meetings eminent scholars and experts who, in an informal way, present to the Committee their particular knowledges and opinions in a variety of fields related to medicine. The presentations of the speakers are freely discussed by the members, the Committee seeking, in this way, to acquire a broad view of the social, educational and scientific factors that enter into the problems with which it is concerned.

It is the object of the Committee to obtain broad, historical perspectives so that we at the Academy may better envisage the form of society into which the world is being rapidly projected and be the better able to help adapt medicine, in all of its many phases, to the new world pattern.

Our first year of study has convinced us that the social pattern of the immediate future will be influenced by planning on the part of the government, industry, labor and consumers and that the Academy can and must play an active part in the adjustment of medicine and public health to this new social order.

In the development of its work, the Committee has undertaken the preparation and publication of a series of monograph studies devoted to the major individual problems affecting the structure and functions of the medical profession. Now in the process of preparation are monographs dealing with American Medical Practice; The American Hospital; Medical Research; Industrial Medicine; Labor Medicine; The Various Types of Insurances for Medical Services; and Preventive Medicine. Additional monograph studies are planned to deal with Medical Education; Rural Medicine; The History of the Development of the Specialist and its Relations to Group Practice; The Development of the Community, State and National Medical Services; Dentistry; Nursing; Convalescent Care; Psychosomatic Medicine, and Medical Social Service.

The Committee expects that the materials provided by these monographs, together with the subject matter gleaned from its weekly conferences, which are to be continued through 1944, will provide it with

the substance of its final report.

An Editorial Committee, consisting of Dr. Iago Galdston, Mr. Lawrence Frank and Professor Bernhard J. Stern, has begun to prepare the outline of the Committee's Final Report. This report we hope to have finished during 1944, and it is our expectation that it will offer fundamental data and concrete help toward the solution of the problems in medical service which we in medicine must thoughtfully and courageously face.

We are satisfied that our Committee on Medicine and the Changing Order has made good progress during this, the first year of its existence.

Despite our earnest concern with the future, we have not neglected the present and we have met, to the best of our abilities, the added and emergency demands which the war has placed upon us. We have yielded no ground, despite losses in budgetary resources, in fellowship and in personnel. Our Stated Meetings, our Friday Afternoon Lectures, our Annual Graduate Fortnight, our Laity Lectures, in a word, all our educational services to the profession, as well as to the public, have been carried on without remission. In addition, we have had the opportunity to render a number of new services.

The war, as you know, has placed a heavy burden upon our transportation system. Because of that, and at the request of the government, most national scientific organizations have suspended their annual conferences. Yet it is vitally necessary that the workers in science should meet in common periodically, to exchange in person, their views and experiences. Such cross fertilization of the intellect assures the best yield in the fields of science. Since, then, national meetings are impossible, a number of regional meetings could serve the same ends. For this purpose our Committee on Medical Education arranged, in May, 1943, a Conference on Clinical Research.

This conference brought together the research workers of Metropolitan New York for a review and discussion in common of their work and problems in a variety of fields, particularly in medicine, surgery, obstetrics and gynecology. This conference was conducted simultaneously in three separate halls, included twenty-seven presentations and was attended by 500 participants. In this way our Committee on Medical Education helped to overcome the handicaps suffered by the research workers in the war time cancellations of the customary meetings of scientific organizations.

Nor has our Committee on Medical Education remained unmindful of the Challenge of the Future, particularly as it involves medical education. The accelerated medical course which is now being given to thousands of medical students, the curtailment to nine months duration of hospital internships, the restrictions placed upon residencies and other forms of postgraduate instruction and training, dictated by the demands of the war, threaten to unloose upon the public, once peace is established, a host of inadequately trained physicians. No one, may I add, is more acutely aware, and more anxious about the inadequacy of their education and training than the young medical men affected. To this grave problem our Committee on Medical Education is giving most earnest thought and study. It is formulating plans for postgraduate education of the war time graduates in medicine, as well as for the thousands of other physicians who will have been out of civil practice for a number of years.

The Committee on Medical Education furthermore fully realizes the extraordinary opportunity and the momentous responsibility, which now confront medical education in New York City. Devastation, yes, even annihilation has overtaken the chief European centers of medical education. Years, perhaps decades must elapse before these centers can be restored or reestablished. In the present and immediate future the medical men of all the world, and particularly the twenty-one republics of Central and South America and West Indies, must turn to America, and to a great extent, to New York City for leadership in the medical sciences.

The Committee on Medical Education realizes the pressing actualities of these demands and has given much thought to an appraisal of our resources to meet these needs. New York has, beside the Academy, five great County Medical Societies, five medical schools, and more than two hundred modern hospitals, numerous excellent clinics, and many distinguished teachers and practitioners in the medical sciences. The problem of organizing and utilizing our splendid resources is indeed made more difficult by their very multiplicity. If we are successfully to employ all available means for postgraduate medical education, we need leadership, organization, and coöperation.

This problem is rendered the more perplexing by two additional factors; the one is the certainty that post-war demobilization of our military and naval forces will multiply a hundred-fold the demand for shorter

refresher courses for our own demilitarized doctors; the other is the uncertainty arising from proposed basic changes in our laws governing social economy and medical practice.

The Committee on Medical Education is now searching for an adequate solution: Will the present universities and other teaching institutions be able to expand sufficiently to meet these great demands? Will it be necessary to establish a new and independent school for postgraduate medical education? Or will it be possible for the Academy, working with the medical schools, the County Medical Societies and the great teaching hospitals, to develop an adequate, coöperative organization which will effectively employ our unsurpassed resources for medical education?

A solution is not easily found, yet the Committee feels that central leadership, and complete, unselfish coöperation of all parties will yet provide one.

Of the many other services rendered by the Academy, I can highlight only a few. The Public Health Relations Committee, at the request of the Mayor, has completed an extensive study on the effects of marihuana. The Committee also is working on a study of adolescent boys and juvenile delinquency.

For many weeks the Committee has been studying the details of the organization of the War Industries Training Program and has developed standards for physical fitness for trainees, both men and women, in the various war industries. This has been made the basis for the procedure which is being carried on by the Department of Education in coöperation with the federal authorities.

Early in the year, the Committee issued a report on oleomargarine which helped considerably in removing certain administrative and legislative obstacles in the way of oleomargarine production and has helped to make it a requirement that each pound of oleomargarine contain at least 0.000 units of vitamin A.

The Committee has been helpful in bringing about a meeting of minds in the establishing, formulating and developing of a program for the training of practical nurses. This has helped to obtain the necessary agreements in the field and a budget for the development of this important accessory group of nurses.

In response to a request from a member of the State Grievance Committee, a great deal of time has been given to the study of the present

law concerning abortions and suggestions have been made for legislative change which would close the various technical loopholes that have been made use of by those who perform criminal abortions.

Turning now to still other of the Academy's accomplishments during the past year, we can cite with satisfaction, the aid rendered to the U. S. Public Health Service. The Academy's facilities were placed at the disposal of the United States Public Health Service for a period of six days, during which twelve lectures were given on Occupational Dermatoses. These lectures were largely attended by members of the medical profession in the Army and Navy, particularly those connected with the government manned ordnance plants.

Office space in the Academy was allotted to the Bureau of Procurement and Assignment.

The Fourth Annual Health Education Conference of the Academy was this year devoted to radio. It was attended by one hundred and seventy participants, representing over ninety separate organizations, including representatives of six of the largest broadcasting systems. The problem approached was that of a more effective collaboration with radio in the education of the public in preventive medicine.

The lectures before the Stated Meetings on penicillin, the sulfonamide derivatives and the Lectures to the Laity on "The Methods Of Combating Tropical Diseases Arising From The War," were outstanding.

The election of fifty-two corresponding Fellows in Latin American countries in 1942 resulted in the creation of much good will. The Committee on Medical Education is now also preparing a list of outstanding medical men in the Soviet Union for Fellowship in the Academy.

The establishment of the Florence Ellsworth Wilson Memorial Fund will give us an income of invaluable assistance in obtaining outstanding speakers for the Graduate Fortnight.

The intensified interest of the public in health matters has been a tax upon the personnel and the physical capacity of the Library. The most urgent need of the Academy is for funds which will enable us to meet these demands on our Library, which stands alone, due to the war's devastating effect on so many of the great medical libraries of the world. We must not only be guardians of the intellectual treasures of the past, but we must have available to all who seek knowledge after the war, the most complete records of the medical advances of this period.

The activities of the Academy have actually increased in spite of rigid economies necessitated by the marked increase in operating costs. Our deficit for 1943 was approximately twelve thousand dollars. This represents almost the exact amount lost through admission fees and the cancelled dues of the 322 Fellows now in military service. In this connection I am happy to report that one of our prominent Fellows has again come to our aid with a contribution that effaced our deficit. But I am obliged to advise you that the budget for 1944 does not permit of overdue salary adjustments nor does it allow adequate funds for the purchase of medical books or periodicals for the Library.

The Steering Committee has done and is doing an outstanding work in endeavoring to provide funds that the Academy may continue its invaluable activities and attain its objectives.

These, then, are our achievements: We have clearly formulated our objectives. We are earnestly seeking to anticipate the form of society in which we shall live. We are in the process of adjusting medicine, in its broadest sense, to the new social order. In addition, we have carried on the regular activities of the Academy at a high level and we are meeting those problems arising from the war.

We feel that the year 1944 offers the Academy the greatest opportunities for service in its long and distinguished history, and we are determined that its magnificent work shall never falter, but go on to greater fulfillment—for—

“Time is our Slave and Fortunes.
We need not years for fruition,
Here in our hands behold the key,
Which unlocks the world.”

THE TREATMENT OF LOBAR PNEUMONIA AND PNEUMOCOCCAL EMPYEMA WITH PENICILLIN*

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THE therapeutic value of penicillin for patients was first described in the treatment of cases of staphylococcal infection.¹ Even though penicillin has not been found in tests in the laboratory to be as potent in antibacterial action against staphylococci as against pneumococci or hemolytic streptococci, it is, nevertheless, more effective against staphylococci than are the sulfonamide drugs. Consequently, the fact that clinical trials were first attempted in cases of severe staphylococcal sepsis constituted a rational procedure and subsequent experience has yielded highly satisfactory results in this type of infection that has not been uniformly amenable to sulfonamide therapy.^{1,2,3}

In accord with experimental studies which have demonstrated the antagonistic action of penicillin against a wide variety of pathogenic bacterial species, estimates of the value of penicillin therapy have been broadened beyond cases of staphylococcal etiology to include many different kinds of infection in man. The most recent results have been recorded and summarized in the comprehensive report of Keefer, Blake, Marshall, Lockwood, and Wood.³

The present report is limited to a description of the results obtained in the treatment of pneumococcal pneumonia and pneumococcal empyema with penicillin.

The unusually high degree of antibacterial activity of penicillin, *in vitro*, against pneumococci was demonstrated in the original report of Fleming⁴ and has been repeatedly observed by others.^{5,6,7} *In vivo*, the curative action of penicillin in mice has been demonstrated against many

* The investigation of empyema was aided through the Commission on Pneumonia, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of The Surgeon General, United States Army.
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hundred thousand lethal doses of highly virulent strains of different serological types of pneumococci.^{8,9} Although some variation in the sensitivity of strains has been suggested, pneumococci appear to be one of the pathogenic bacterial species most vulnerable to the action of penicillin.

When the experimental results just mentioned are taken into account in connection with the proven low toxicity of penicillin for man, the favorable outcome of the treatment of pneumococcal infections with penicillin becomes a reasonable expectancy.

Forty-six cases of pneumococcal pneumonia and 8 cases of pneumococcal empyema comprise the present series. In view of the fact that the methods of treatment and the details of the study of the cases of pneumonia and of the cases of empyema were different, each of the subjects is presented separately.

I. THE TREATMENT OF PNEUMOCOCCAL PNEUMONIA WITH PENICILLIN

Although the number (46) cases of pneumonia is not great, the selection of patients to be treated with penicillin was limited to those who, on admission, exhibited lobar consolidation and a degree of severity indicating the probable pneumococcal etiology of the infection. Even though therapy was at times instituted before the bacteriology was reported there were only three instances in which the specific etiology was undetermined. The data in Table I on the distribution of serological types of pneumococci responsible for the infections and also the incidence of bacteriemia indicate that the cases used for treatment consisted of a representative sample of pneumococcal pneumonia with respect to kind and severity.

In the patients with pneumonia the observations have been directed not only toward determining the value of penicillin as an effective curative agent but the attempt has also been made to estimate the range of dosage that was sufficient without constantly employing amounts that might be excessive and, therefore, unnecessary. For this latter purpose the number of injections and the duration of treatment were arbitrarily altered in order to observe the response to limited treatment.

Material and Route of Administration. The penicillin was supplied in a dry powder contained in sealed ampoules. It was kept constantly in the ice box. Solutions for injection when prepared in advance were also kept in refrigeration but were not retained for longer than a day

or two. It may be noted in passing that solutions used in the laboratory for experimental purposes have been found to retain potency for several weeks.

Penicillin in solution was given to patients by repeated injections either intravenously or intramuscularly. For intravenous injection the powder was dissolved in physiological salt solution or sterile water in the ratio of 1000 units to 1-1.5 cc. of solution. For intramuscular injection the ratio was 1000 units to 0.3 cc. of solution so that the usual individual dose of 10,000 units was contained in a total volume of 3.0 cc.

Some of the patients were treated solely by intravenous injections, others only by intramuscular injections, and still others received intravenous medication for the first few doses followed by intramuscular injections for subsequent treatments. The intramuscular route proved to be effective and was, for convenience sake, frequently employed. However, in cases which appeared seriously ill on admission, one to four injections were given intravenously and when improvement seemed evident subsequent injections were given intramuscularly.

Dosage of Penicillin and Spacing of Treatment. The amount of penicillin per dose ranged from 10,000 to 25,000 units, most frequently the former. The repeated doses which were given in series were made at three hour intervals.

Several procedures were employed which differed in the following respects:

1. Number of repeated injections at three hourly intervals which comprised one series of treatments. The single series varied from three to eight injections, the latter lasting for twenty-four hours.

2. The lapses between each series of injections which were given from day to day were not always kept constant. Charts are presented which illustrate the clinical courses of patients who received interrupted treatment.

3. The number of consecutive days of treatment varied from one to four. The information which emerged from altering the duration of treatment will be subsequently discussed.

Etiological Pneumococcal Types. From Table I it may be noted that in 32 (69 per cent) of the cases the infecting pneumococci belonged to serological Types I-VIII. Fourteen patients had bacteriemia (30 per cent). Among the cases in which the pneumonia was due to pneumococci, Types I-VIII, 13 (40 per cent) has bacteriemia.

TABLE I
SUMMARY OF CASES OF PNEUMONIA TREATED WITH PENICILLIN

| Pneumo Types | No. of Cases | Blood Culture | Duration of Treatment Days | | | | | Total Dosage of Penicillin (Range) Oxford Units | Definite | Response Indefinite | Died |
|-----------------|--------------------|---------------|-------------------------------|---|---|---|----|--|----------|------------------------|------|
| | | | + | — | 1 | 2 | 3 | 4 | | | |
| I | 11 | 4 | 7 | | 2 | 5 | 3 | 60,000-250,000 Av: 148,000 | 10 | | 1 |
| II | 6 | 3 | 3 | | 1 | 3 | 2 | 70,000-170,000 Av: 113,000 | 6 | | |
| III | 1 | 1 | 0 | | | | 1 | 140,000 | 1 | | |
| IV | 1 | 1 | 0 | | | 1 | | 110,000 | 1 | | |
| V | 5 | 1 | 4 | | 1 | 2 | 2 | 70,000-190,000 Av: 115,000 | 4 | 1 | |
| VI | 2 | 1 | 1 | | 1 | | 1 | 70,000-140,000 Av: 105,000 | 2 | | |
| VIII | 4 | 2 | 2 | | 1 | 2 | 1 | 70,000-120,000 Av: 90,000 | 3 | | 1 |
| IX | 1 | 0 | 1 | | | 1 | | 120,000 | | | 1 |
| XI | 2 | 0 | 2 | | 1 | | 1 | 40,000-130,000 Av: 85,000 | 2 | | |
| XII | 1 | 0 | 1 | | | 1 | | 90,000 | 1 | | |
| XV | 1 | 0 | 1 | | | 1 | | 120,000 | 1 | | |
| XIX | 1 | 0 | 1 | | | 1 | | 90,000 | 1 | | |
| XX | 1 | 1 | 0 | | 1 | | | 50,000 | 1 | | |
| XXIX | 1 | 0 | 1 | | | 1 | | 95,000 | | 1 | |
| Unclass. | 7 | 0 | 7 | | 2 | 1 | 3 | 30,000-160,000 Av: 100,000 | 5 | 2 | |
| TOTAL | 45 | 14 | 31 | | 4 | 7 | 21 | 30,000-250,000 Av: 105,000 | 38 | 4 | 3 |

Outcome of Treatment. Among the 46 patients treated with penicillin, three died. (Mortality 6.5 per cent). Of the patients who died, one was a 69 year old man who had severe congestive heart failure together with pneumonia and bacteriemia due to pneumococcus, Type VIII. His blood culture, taken on the second hospital day, was sterile and his temperature was below 100°F. but the heart failure was worse. He died 36 hours after admission. The second fatal case had pneumonia and bacteriemia, pneumococcus, Type I, superimposed on some chronic pulmonary disease. His blood culture of the second hospital day was sterile but there was no clinical improvement. Subsequent therapy included sulfadiazine and antipneumococcus serum, Type I, but it was ineffectual. The third fatal case had pneumonia due to pneumococcus, Type I, but no bacteriemia. He did not appear severely ill but did not respond to penicillin. He died on the third hospital day a few hours after pulmonary edema developed.

Of the 43 patients who recovered, in four instances therapy was not followed by rapid clinical recovery. The result is, therefore, listed as indefinite, although the final diagnosis in one patient was primary atypical pneumonia and the other three had prolonged courses, in one of whom there was delayed resolution which was unexplained; in another, who after several weeks developed pneumothorax, tuberculosis was suspected; and the third patient had bronchiectasis on which the pneumonia was superimposed. Even though these three latter cases are classed as ineffectively treated, the sterilization of the bacteriemia by penicillin in two of them will be subsequently mentioned.

The remaining 39 patients (84 per cent) recovered in a manner that indicated the high degree of effectiveness of penicillin.

The rapidity in the drop in temperature was striking, the change occurring usually within the first 12 to 20 hours, and the impression was that the response occurred somewhat more quickly than that observed after sulfonamide therapy. The alleviation of symptoms was marked. The respirations were slowed to normal rates coincident with improvement although cough persisted for several days. There were no untoward depressive physiological reactions referable to the rapid critical change in the condition of the patients. Although no data have been collected with regard to the rate with which clearing of the consolidated area occurred, the impression has been formed that resolution progressed more rapidly than that observed following sulfonamide therapy.

The leukocyte count was unaffected by penicillin and returned to normal within four to six days.

No toxic reactions were observed, except an occasional pyrogenic reaction which came on about one hour after an injection and lasted approximately two hours. The degree of soreness at the site of intramuscular injection was never severe, nor was there any swelling or redness or appreciable local irritation.

The hematopoietic system exhibited no signs of irritation. No special changes in urine were noted. No psychic or neurological abnormalities were evident.

Duration of Treatment. From an analysis of the data given in Table I under the heading "Duration of Treatment, Days," information is available concerning the length of time that therapy may be required. In all of the patients without complications an initial definite response was noted within 16 to 20 hours of beginning treatment as evidenced by sharp drop in temperature and symptomatic improvement. The subsequent course varied, however, depending on the length of time treatment was continued.

From Table I it may be seen that most of the patients, 31, were treated for 3 to 4 days. Among this group, when no complicating factors existed, the initial improvement persisted as permanent cure.

The complications which delayed prompt and complete recovery were empyema and chronic pulmonary disease on which pneumonic consolidation was superimposed. Among the cases with complications other than empyema it may be stated that when treatment was switched to sulfadiazine no appreciable response was obtained.

Clinical Response in Relation To Dosage. In attempting to estimate the amount of penicillin necessary to suppress the infection, the injections in selected patients were arbitrarily interrupted after the first or second day of treatment. Most of the patients in these groups received 30,000 to 40,000 units per day in divided doses of 10,000 units each. The reaction of the infection to the measured treatment has served as a source of information with regard to the degree and duration of the response in relation to quantity of the drug.

Table II contains data derived from patients in whom injections of penicillin were arbitrarily withheld following either one or two days of therapy. An analysis of the material in Table II reveals the following:

In each of the seven cases in which penicillin therapy was adminis-

TABLE II
COURSE OF PATIENTS IN WHOM ADMINISTRATION OF PENICILLIN
WAS INTERRUPTED AFTER ONE OR TWO DAYS OF THERAPY

| Patient | Admin. Day of Disease | Pneumonia Type | Blood Culture | Penicillin—1st Day | | Penicillin—2nd Day | | Initial Response | Subsequent Course |
|---------|-----------------------------|-------------------|------------------|----------------------|-----------------|----------------------|-----------------|---------------------|----------------------|
| | | | | No. of Injections | Daily Amount | No. of Injections | Daily Amount | | |
| J. Z. | 3rd | Unclassi- fied | — | 3 | 30,000 | — | — | Yes | Rapid Recovery |
| M. H. | 3rd | VII | — | 3 | 30,000 | — | — | Yes | Relapse |
| D. R. | 2nd | Unclassi- fied | — | 4 | 40,000 | — | — | Yes | Rapid Recovery |
| V. J. | 2nd | XI | — | 4 | 40,000 | — | — | Yes | Rapid Recovery |
| B. M. | 3rd | II | — | 4 | 40,000 | — | — | Yes | Relapse |
| F. T. | ? | XX | + | 5 | 50,000 | — | — | ? | Prolonged |
| J. G. | 3rd | VIII | — | 7 | 70,000 | — | — | ? | Died |
| L. T. | 4th | II | — | 4 | 40,000 | 3 | 30,000 | Yes | Rapid Recovery |
| A. K. | 3rd | V | — | 6 | 60,000 | 3 | 30,000 | Yes | Relapse? |
| J. B. | 5th | II | — | 4 | 40,000 | 4 | 40,000 | Yes | Relapse? |
| A. L. | 3rd | Unclassi- fied | — | 4 | 40,000 | 3 | 30,000 | Yes | Relapse |
| E. F. | 1st | II | + | 4 | 40,000 | 5 | 50,000 | Yes | Relapse |
| M. B. | 4th | V | + | 4 | 40,000 | 5 | 25,000 | Yes | Empyema |
| O. B. | ? | I | + | 3 | 30,000 | 3 | 30,000 | ? | Died |

tered on the first day and then interrupted, there was a significant drop in temperature to below 101° in 16 to 24 hours but permanent cure was not uniformly effected.

In each of the two patients in the one day group with bacteriemia a second blood culture taken on the second hospital day was sterile.

With the exception of the patient who died 36 hours after admission, symptomatic improvement accompanied the early fall in temperature.

Complete cure followed a single series of injections given for one day in three cases. However, it should be noted that the pneumococci isolated from their sputum belonged to serological types not usually associated with severe pneumonia. Consequently, the mildness of the pneumonia may have promoted the striking response even though the patients were treated early in the disease, i.e., 3rd, 2nd and 2nd days respectively.

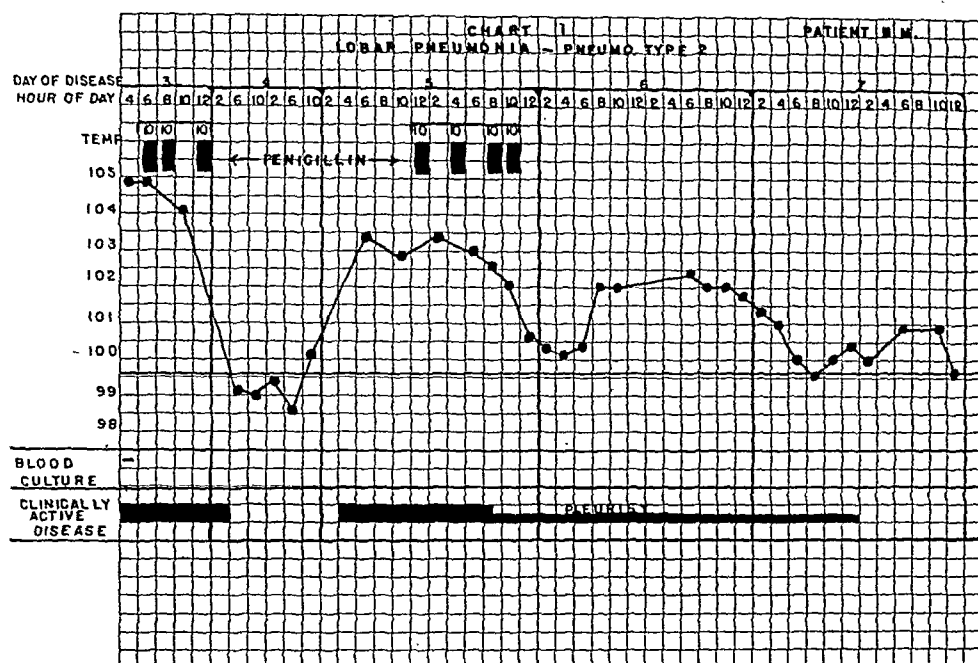
In the three remaining cases who recovered and in whom treatment was withheld after the first day, a relapse of the infection occurred. Recovery, however, promptly followed the reinstitution of treatment.

In the patients who were treated on *two consecutive days* before withholding therapy, with the exception of the fatal case, improvement followed the first day of therapy. Consequently, the second series of injections was given after improvement had begun. In each instance of bacteriemia in this group, the blood culture taken on the second day was sterile and remained so.

As to the final outcome following two days of treatment one of the patients made a rapid and permanent recovery, whereas, among the remaining cases in this group, two had transient rises of fever to 101° to 102° appearing 48 hours after the last injection and spontaneously receding within two days, and the other two had definite relapses.

From a consideration of the findings given in Table II it appears that penicillin in the dosages employed evoked rapid early improvement indicating the high degree of sensitivity of the infecting pneumococci to penicillin. It is also evident that relapse was liable to occur if treatment was not extended longer than two days.

From the standpoint of chemotherapy the importance of the development of type specific immunity in promoting permanent recovery from pneumococcus infections has been illustrated both experimentally and clinically in relation to sulfonamide therapy. MacLeod¹⁰ demon-

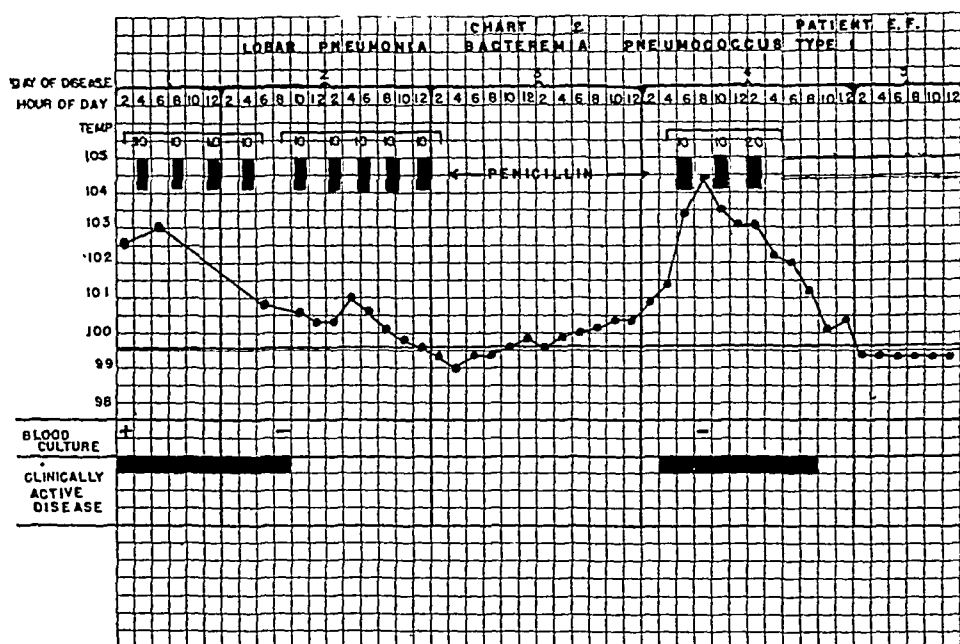


strated in mice that the suppression of pneumococcal infection by sulfa-pyridine was made permanent by the appearance of type specific immunity. In pneumonia the observation has been repeatedly made that patients treated early (first to third day) with appropriate sulfonamides are liable to relapse if treatment is stopped in one or two days.

In comparing the experience with sulfonamides with that encountered with penicillin it seems probable that the continuance of treatment as determined by the day of disease is of equal importance with either of the drugs.

For purposes of demonstrating graphically the quantitative relationships between dosage and its effect on the infection with particular reference to the duration of the remission after premature withdrawal of treatment, the details of the courses of two patients are given in Charts 1 and 2.

Chart 1 is that of a patient with pneumonia due to pneumococcus, Type II, who was admitted on the 3rd day of disease. Following the details of the temperature chart it may be seen that the last dose of penicillin on the first day was given at approximately 12 midnight and that the temperature became normal between 2 and 6 the following morning—12 hours after beginning therapy. That the therapeutic effect



was not solely antipyretic is evidenced by the marked alleviation of symptoms during the afebrile period. The patient became worse at about 4 o'clock on the morning of the 3rd hospital day, approximately 28 hours after the last injection. In view of the fact that measurable amounts of penicillin have been found by Rammelkamp and Keefer¹¹ to disappear from the blood within 3 hours after injection, the disease in this patient was restrained for approximately 25 hours after the blood level of penicillin was presumably zero.

The second series of injections of penicillin given on the 3rd hospital day was also followed by a definite response. A dry pleurisy persisted for two additional days but complete recovery was not further delayed.

Chart 2 is that of a patient whose course was particularly instructive. He was admitted eight hours after a chill which initiated the attack of pneumonia. Injections of penicillin were begun promptly. His blood culture was positive for pneumococcus, Type 1. His course illustrates the importance of taking into account the day of disease on which therapy is begun in determining the duration of therapy. In this patient two series of injections on two consecutive days were given before withdrawal of treatment. His response to the first four injections of the first

day occurred, as indicated in Chart 2, within 16 hours. A second blood culture taken five hours after the last previous injection of penicillin was sterile. The initial early improvement was maintained for approximately 28 hours after treatment was stopped. A relapse then occurred abruptly, although a blood culture taken at the height of the febrile exacerbation was negative.

Penicillin therapy was again instituted on the fourth day. Subsequently in this case sulfadiazine was given as supplementary treatment during the latter part of the fourth day because the patient was encountered early in the trials of penicillin before its efficiency for pneumonia had been well established. Permanent recovery occurred on the 6th hospital day.

The course of the two patients just described, in addition to illustrating the rate of response, also demonstrates the duration of the period of remission after premature interruption of treatment.

Results comparable to those just described have been observed in other patients who were followed in a similar manner. In summary, they indicate that, in the average uncomplicated case of pneumonia, the administration of 30,000 to 40,000 units per day in divided doses initiates improvement. Furthermore, the remission evoked by the therapy endured for approximately 20 to 28 hours before the effect of the penicillin was lost.

These findings have afforded useful information in formulating a complete course of treatment with respect to quantity and spacing of dosage.

Additional data of a similar character have been derived from an analysis of the course of the patients with bacteriemia in relation to the injections of penicillin which they received.

Effect of Penicillin on Bacteriemia. Fourteen of the patients had bacteriemia on admission. In each instance following penicillin therapy the second blood culture was sterile. In seven of the patients the time relationships between the second blood culture and the last previous dose of penicillin is sufficiently definite to offer information concerning the duration of the sterilizing effect. The findings are contained in Table III.

The quantitative range of dosage during the first 24 hours in this particular group of bacteriemic cases was from 30,000 to 105,000 units. The differences in amounts of penicillin that were administered oc-

TABLE III
AMOUNT OF PENICILLIN EFFECTIVE IN ALTERING BACTEREMIA*

| Pneumo Type (Patient) | 1st Blood Culture | Amt. of Penicillin before 2nd Bl. Culture Units | Route of Administration | 2nd** Blood Culture | Interval between previous dose of Penicillin and 2nd Blood Culture |
|--------------------------|-------------------------|---|--|---------------------------|--|
| I (J. S.) | + | 105,000 | 75,000 Intravenous 30,000 Intramuscular | — | 3 hrs. |
| I (J. St.) | + | 90,000 | 25,000 Intravenous 65,000 Intramuscular | — | 5 hrs. |
| II (M. L.) | + | 60,000 | Intravenous | — | 6 hrs. |
| II (E. F.) | + | 40,000 | Intravenous | — | 9 hrs. |
| III (B. R.) | + | 40,000 | Intravenous | — | 5 hrs. |
| VIII (J. G.) | + | 60,000 | Intravenous | — | 16 hrs. |
| I (O. B.) | + | 30,000 | Intravenous | — | 10 hrs. |

*In the six other cases which had bacteremia on admission the 2nd blood culture was sterile, but it was not taken until the 2nd or 3rd day of hospitalization.

**In each instance the 2nd blood culture was taken approximately 20-24 hours after the 1st.

curred for the most part in connection with explorations of dosage which was altered as experience developed. That the blood stream was cleared in each instance is striking evidence of the potency of penicillin in its antipneumococcal action.

It is of further interest to note from Table III the time of the last previous dose of penicillin in relation to the time of taking blood for the second culture. From the figures in the table it may be seen that intervals of from 3 to 16 hours elapsed but that the bacteriemia did not return. By the method which they employed, Rammelkamp and Keefer¹¹ found that penicillin was detectable in the blood for 30 to 210 minutes after intravenous injection, the time varying according to the dosage of the drug. On the basis of the figures of these authors, it may be estimated that, in the bacteriemic patients described in Table III, the initial clearing of the blood was maintained in different patients for varying periods of time up to at least 13 hours after circulating penicillin was presumably no longer detectable. Consequently, the damaging effect of penicillin on the invasive pneumococci appears to have restrained their regrowth for an appreciable period after the blood level ceased to be measurable.

Each of the patients of Table III received penicillin intravenously. Whether the rapidity and persistence of the clearing of the blood of pneumococci is best accomplished by intravenous medication has not been determined since comparable studies have not been made following intramuscular injections. The findings in the bacteriemic cases when combined with the results illustrated in the previous Tables and Charts suggest that the maintenance of a definite level of penicillin continuously may not be a necessary detail of satisfactory treatment.

DISCUSSION OF FACTORS INVOLVED IN THE APPLICATION OF PENICILLIN TO THE TREATMENT OF PNEUMONIA

Duration of Treatment. On the basis of the experience described in this article it seems apparent that in order to avoid relapses, treatment should be extended over three or four days or for longer periods under special conditions. As stated earlier the duration of treatment is influenced by the day of the disease on which it is started since a remission effected early in the infection (first to third day) may not be maintained unless treatment is continued until the elements of immunity or other factors in the evolution of the disease become operative.

With regard to continued repetitions of injections the data have indicated that when an interval of 12 to 16 hours was permitted to elapse between daily treatments the results were as satisfactory as those obtained by maintaining therapy throughout 24 hours. The special studies demonstrate that the arrest of the infection caused by penicillin was continued beyond the period during which penicillin would be expected to be detectable in the circulating blood.

The reports of Florey and associates¹ and of Rammelkamp and Keefer¹² have described the rapid excretion of penicillin in the urine and also the distribution of the drug in normal body fluids following parenteral injection. However, the extent to which penicillin penetrates into inflamed areas, or the concentration or the persistence of the product in an active state in the extravascular sites of the infection within tissues has not been determined. Whether or not alterations in permeability and diffusion which membranes undergo as a result of inflammation affect the dissemination of penicillin has not been determined.

In interpreting the protracted effect by which the abatement of the infection persisted after the disappearance of circulating penicillin, it seems possible that the result may be dependent upon the retention of penicillin at the local site of the infection for a longer period of time than in the circulating blood, or that the damage inflicted by temporary contact between penicillin and pneumococci is sufficiently severe to delay the further multiplication of organisms.

On the basis of the response of patients, therefore, four injections daily at three hour intervals on three to four successive days has proved satisfactory.

Route of Injection. For the cases of relatively moderate severity, the intramuscular route of injection has been found to be efficacious. However, in patients appearing seriously ill or in those with bacteriemia, the results following intravenous therapy as measured by clinical improvement and disappearance of bacteriemia (Table III) indicate the effectiveness of the intravenous route, which may be preferable for the first few injections.

Amounts per Dose. 10,000 units have been the routine amount employed for intramuscular injection. 10,000 or 25,000 units have been given in intravenous injections, depending on the severity of the case.

Suggested Plan of Treatment. Consolidating the findings that have

been discussed above, the following procedure is tentatively outlined.

Cases of Moderate Severity: 10,000 units of penicillin given intramuscularly every three hours for four doses on each of three and possibly four successive days.

Seriously Ill Cases: 25,000 units given intravenously every three hours for the first two doses of the first day, followed by 10,000 units intramuscularly at three hour intervals for the second two doses of the first day. Subsequent treatment of the second, third, and fourth day to follow plan outlined for cases of moderate severity, i.e., four doses of 10,000 units every three hours for each day.

It is obvious that variations in the clinical course of individual cases may require special alterations in treatment. It should also be emphasized that the above suggestions are not presented as established recommendations but that they represent a current appraisal based on the objective data contained in this report. In view of the low toxicity of penicillin, more extensive therapy than that outlined may be employed without the hazards of serious reactions. However, this study has been directed toward an attempt to define quantitatively the relation of clinical response to therapeutic dosage.

Comparative Value of Penicillin and Sulfadiazine in Pneumonia. Our experience indicates that the therapeutic value of penicillin in pneumonia is at least equal to that of sulfadiazine, and, in addition, there are certain well defined conditions that make the use of penicillin particularly advantageous. They may be summarized as follows:

1. The fact that, up to the present time, no significant toxic manifestations have been noted in association with the administration of penicillin is of special interest. A few cases of urticaria have been described⁸ (none in the present series) but the evidence is inconclusive that the eruptions were based on the development of sensitivity. It is, furthermore, uncertain whether such reactions were caused by penicillin or by some contaminating ingredient present in the preparations.

2. Penicillin is particularly serviceable when pre-existing sensitivity to the sulfonamide drugs contraindicates their use, or when sulfonamide toxicity develops during treatment before the infection has been completely overcome.

3. Penicillin has been shown experimentally to be highly effective against sulfonamide-fast pneumococci.^{9, 12, 13} In the second part of this article which deals with the local use of penicillin in the treatment of

empyema, the value of penicillin in patients suffering from infections caused by sulfonamide-resistant pneumococci will be described.

It is also of interest to record briefly the favorable response to penicillin of two patients with lobar pneumonia and bacteriemia due to pneumococci refractory to sulfadiazine.

One of the patients in the present series was admitted to the hospital on the seventh day of pneumonia after having received sulfadiazine continuously from the beginning of his illness but without improvement. On admission, in addition to lobar consolidation, he also had bacteriemia due to pneumococcus, Type VII, and a blood level of sulfadiazine of 6.6 mgms. per cent which remained from the pre-admission treatment. By laboratory tests the strain derived from the blood culture proved to be sulfonamide-fast.

Under penicillin therapy the blood culture became sterile within 24 hours and the patient recovered uneventfully in spite of the fact that he also had lymphatic leukemia.

A second instance of infection with a sulfonamide-resistant strain of pneumococcus successfully treated with penicillin was that of a 63-year-old female* who had had pneumonia and an intermittent bacteriemia due to pneumococcus, Type VIII, for approximately 4 weeks before penicillin therapy was instituted. Early in her disease she also developed empyema which was treated surgically by rib resection and drained satisfactorily. She had received sulfadiazine continuously for 4 weeks without permanently altering the bacteriemia. She had also received Type VIII antipneumococcus serum with only temporary improvement. There were no definite signs of endocarditis. On the day following the first injection of penicillin her blood became sterile and remained so. The pneumonia subsided.

In laboratory tests the pneumococci from both the blood culture and the empyemal pus were found resistant to sulfadiazine.

4. Although as yet unsubstantiated by objective data, it seems likely that penicillin sterilizes the blood stream in cases of bacteriemia and suppresses the active infection at a more rapid rate than does sulfadiazine. Although in many instances this difference may not be of special significance, nevertheless in cases of unusually severe infection, the speed of effect may be particularly desirable.

* This case was under the care of Dr. Robert C. Schleusner at the Lenox Hill Hospital and is reported with his permission.

Even though the use of penicillin has the definite advantages just mentioned, the extent to which its widespread use in large numbers of cases of pneumonia would markedly alter mortality statistics is not clear. Analyses of causes of death in cases of pneumonia treated with the sulfonamide drugs¹⁴ have brought out the fact that the majority of the fatalities are due to a variety of complicating circumstances that would not in themselves be overcome even by a more potent anti-pneumococcal drug.

II. THE TREATMENT OF PNEUMOCOCCAL EMPYEMA BY THE INTRAPLEURAL INJECTION OF PENICILLIN

This study of pneumococcal empyema has been directed toward determining the possible usefulness of chemotherapeutic agents introduced locally as a medical method of treatment which might obviate surgical intervention. In spite of the fact that there seems to have been a decrease in the incidence of empyema caused by pneumococci since the introduction of chemotherapy for pneumonia, the administration of the sulfonamide drugs either by mouth or intravenously has not proved satisfactory in the treatment of empyema after the complication has developed.

At the beginning of the present inquiry observations were made on the course of empyema following the intrapleural injection of sulfadiazine. As a curative measure the initial attempts were unsatisfactory since the pneumococci causing the pleural infections were found to retain viability in the presence of large amounts of the drug and the patient's illness remained unchanged. Consequently, penicillin was employed for local injection.

Up to the present time eight patients with pneumococcal empyema have been treated by the introduction of solutions of penicillin into the infected pleural space. The empyemata, with one possible exception, developed as a complication of lobar pneumonia.

Although the details of this report deal with the efficacy of penicillin introduced locally into the empyemal cavities, before proceeding with a description of the methods and results, it is of interest to record briefly some of the observations which were made in connection with local sulfonamide therapy.

The findings are illustrated by the course of one of the patients who was first treated with sulfadiazine and later with penicillin injected

intrapleurally (See Chart 3). After the introduction of sulfadiazine into the empyemal cavity of this patient the sulfonamide content of the exudate reached 415 mgms. per cent. However, on examination of the exudate, pneumococci were seen in direct smears and were viable on culture.

In seeking an explanation for the inactivity of the drug against the organisms as exemplified in the case just mentioned, tests were made for the presence of sulfonamide inhibitors in samples of empyemal exudate obtained from this and other patients. Experiments were also carried out to determine the degree of sulfonamide fastness possessed by several strains of pneumococci derived from empyemal pus.

The results may be briefly summarized as follows:

1. Estimation of the presence of sulfonamide inhibiting substances in pneumococcal pus from cases of empyema.

Five different specimens from four different patients were tested. The method described by MacLeod¹⁵ was employed using a strain of *B. coli* which was cultivated in an inhibitor-free medium in the presence of varying quantities of sulfadiazine. Exudate was then added and its effect on growth observed. The results obtained in each of the tests failed to reveal the inactivation of sulfadiazine by any of the specimens.

2. Tests for sulfonamide-fastness of empyemal strains of pneumococcus.

Six strains from patients with empyema have been tested by *in vivo* methods, which consisted of infecting mice intraperitoneally and treating them with sulfadiazine, *per os*, twice daily for four days. Five of the strains came from the pleural exudate of patients who were treated at the onset of the pneumonia with sulfadiazine. With each of these strains some degree of drug resistance was evident in that an amount of sulfadiazine sufficient to cure mice infected with laboratory strains of pneumococci was incapable of preventing death in mice infected with empyemal strains.

The sixth strain, however, derived from a patient treated from the beginning with penicillin alone had no degree of drug fastness either to sulfadiazine or penicillin.

Although the findings just outlined are too limited to warrant final conclusions, they suggest that, in cases of pneumonia which develop empyema while receiving sulfonamide drugs, the strain derived from

the pleural exudate may exhibit sulfonamide-resistance. On the other hand, if no sulfonamide therapy has been administered, the empyemal strain may be found to be drug susceptible.

That penicillin warranted trial in this type of infection is indicated by the fact that its antibacterial action against pneumococci is equally potent irrespective of the presence or absence of sulfonamide-fast qualities.^{9, 12, 13}

In attempting to develop an effective but uncomplicated method by which penicillin may be utilized locally in pneumococcal empyema, the patients receiving treatment have been studied by correlating their clinical course with the results of laboratory examinations of specimens of pleural exudate derived from the treated area.

The findings have been used as an indication of the degree of effectiveness of varying dosages of penicillin and also as a guide in determining the extent to which repeated injections were necessary.

MATERIAL AND METHODS

In pursuing the studies, samples of pleural effusion were obtained by bedside aspiration at frequent intervals and examined for the presence of viable pneumococci. When pus suspected of containing penicillin was cultured, the specimen was first centrifuged and washed with physiological salt solution in order to avoid transferring a portion of the antibacterial agent contained in the exudate to the broth used for culture media. It may be noted, however, that in comparable tests using 0.1 cc. of specially prepared exudate added to 5 cc. of broth, the preliminary washing did not yield results different from that obtained by adding the same amount of pus directly to the culture media. It seems unlikely that the special technique is necessary as a routine procedure in determining the presence or absence of viable organisms.

In some instances, tests for the presence of penicillin in the exudate were made in order to estimate the duration of its activity following instillation. The method most frequently employed consisted of determining the capacity of the supernatant fluid of centrifuged specimens of effusion to protect mice against infection with pneumococci heterologous in type to that derived from the patient. By this procedure, active penicillin was detected in the exudate for as long as 48 hours after injection in four patients and 72 hours in another patient but was not demonstrable in specimens obtained on the 5th or 6th day following

treatment. As will be discussed later, the duration of sterility has served as a supplementary guide in establishing the quantity and frequency of injections that comprised effective therapy.

Concentration of Penicillin in Solution Used for Injection. Solutions were most commonly made up in a concentration of 1000 units of penicillin in 1 to 1.5 cc. of physiological salt solution. The quantity of solution injected was never in excess of the amount of exudate removed. However, since the largest single dose injected intrapleurally was 40,000 units in 50 cc. and since the amount of exudate aspirated was usually more than 50 cc., the necessity of using a more concentrated solution in order to introduce the desired number of units did not frequently occur. In view of the moderate irritating effect of penicillin on the serous surface of the pleura as indicated in Table IV, the concentration may, under some circumstances, require consideration.

CLINICAL COURSE AND LABORATORY FINDINGS OF THE PATIENTS

The results derived from the study are given in the form of a brief resume of the course of each patient. Charts of four of the patients are included. X-ray photographs, taken before treatment was begun and after recovery, of 6 patients are appended at the end of this article.

Case 1. Patient A.Mc., male, white, age 57 years.

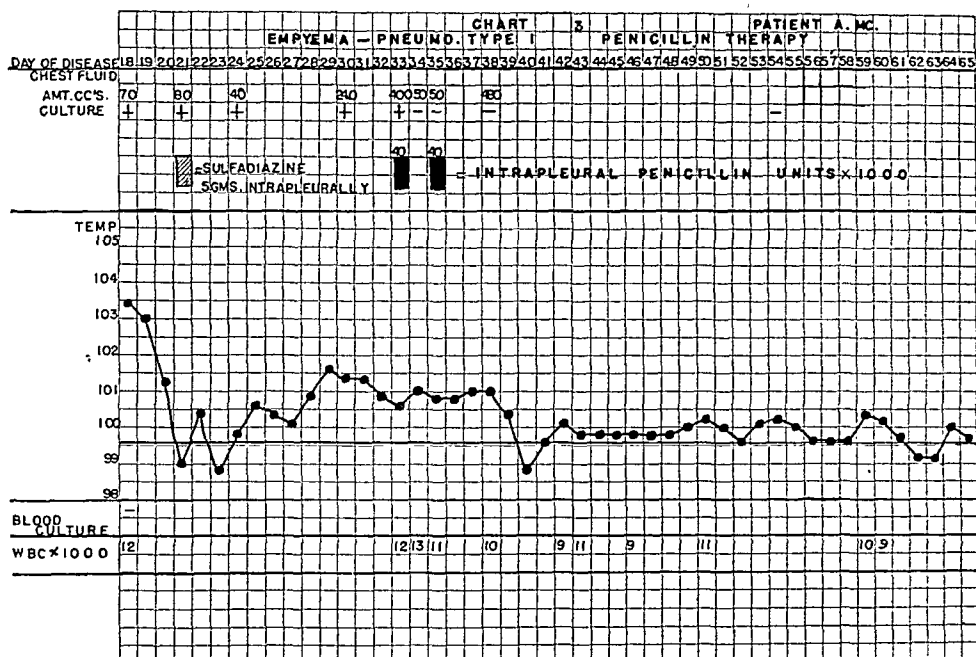
Diagnosis: Lobar pneumonia, bacteriemia, empyema, Pneumococcus, Type 1.

The patient was admitted to our wards on the 21st day of illness. In the early stages of pneumonia he had been treated with sulfadiazine. The blood culture became sterile and pneumonia subsided following sulfadiazine therapy but signs of pleural effusion developed. On three separate occasions during the first two weeks of the patient's illness purulent material containing Type I pneumococci was obtained by thoracentesis. One week after the last of the preceding aspirations the patient came under our observation.

The patient's course is illustrated in Chart 3.

From Chart 3 it may be seen that the local treatment of empyema first consisted of 5 gms. of sulfadiazine injected intrapleurally. As mentioned earlier the failure of sulfadiazine to sterilize the cavity was accounted for by the drug-fastness of the infecting strain.

At the time of the first injection of penicillin 400 cc. of thick puru-



lent exudate containing many pneumococci were withdrawn before introducing 40,000 units contained in 50 cc. of isotonic salt solution.

In a sample of exudate obtained on the day following the first treatment, misshapen gram positive forms were seen in direct smears, but cultures were sterile. In a specimen obtained 48 hours after treatment, no gram positive forms were seen; cultures were sterile. At the time of the latter thoracentesis a second dose was administered consisting of 40,000 units. Although two subsequent samples of pleural exudate were obtained 3 and 17 days respectively after the second treatment, pneumococci could not be seen in or cultivated from either specimen.

From a clinical standpoint the patient's general condition was satisfactory throughout the period of treatment although convalescence was somewhat protracted. A low grade fever (100°F) continued for 30 days. During this period discomfort in his chest was present but was not severe. There were some night sweats and a moderate leukocytosis was maintained. However, when the temperature became normal, the evidences of infection disappeared.

Repeated x-ray examinations of the chest revealed the gradual clearing of a homogenous shadow over the affected area. At a final x-ray examination made two months after discharge from the hospital, the

X-RAY PHOTOGRAPHS OF CASE 1.



Fig. 1 Before penicillin therapy.

Fig. 2 Two months after leaving hospital.

only evidence of abnormality consisted of a small localized band of increased density in the left lateral costophrenic angle.

Resume: Total Number of Intrapleural Injections of Penicillin: Two.

Amount per Dose: 40,000 units.

Total Amount: 80,000 units.

Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery complete with limited residual pleural thickening.

Duration of Hospitalization After Beginning of Treatment: 42 days.

Case 2. Patient E.M., male, colored, age 35 years.

Diagnosis: Lobar pneumonia, bacteriemia, empyema (multiple foci). Pneumococcus, Type VIII.

The patient was treated for the first 10 days with sulfadiazine by mouth. Blood culture became sterile but high fever persisted. Empyema was detected on 6th hospital day. Sulfonamide-fastness of empyemal strain was demonstrated by laboratory tests.

The first intrapleural injection of penicillin (20,000 units) was given on the 10th hospital day. Three additional doses (15,000, 20,000, and 25,000 units respectively) were given into the same site as that of the first injection. The latter treatments were administered on the 2nd,

X-RAY PHOTOGRAPHS OF CASE 2.

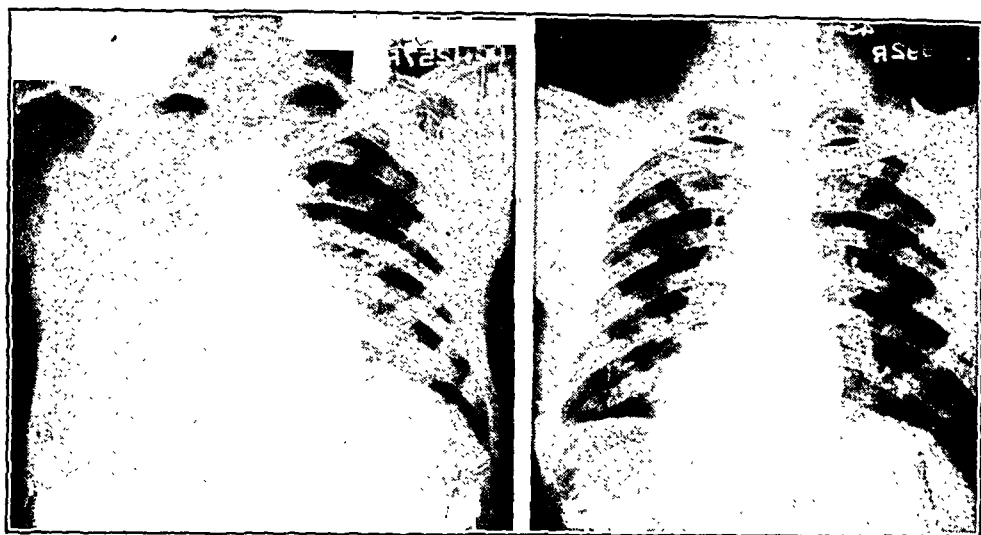


Fig. 3 Before penicillin therapy.

Fig. 4 Four months after leaving hospital.

4th, and 7th day after the initial instillation. Five samples of exudate were taken from the area subjected to repeated treatments between the 1st and 15th day after beginning injections and, in each instance, cultures were sterile.

In spite of the disappearance of pneumococci from the site of infection receiving the repeated injections, the patient continued to be acutely ill. By additional explorations, a second pocket of empyema was found, the exudate from which contained Type VIII pneumococci. Before penicillin therapy was instituted into the second area, the patient began to cough up large quantities of purulent material. The course was interpreted as indicating that the second pocket was being drained through a bronchopleural opening. After 2 weeks the sputum became scanty and ceased to be purulent. The patient was improved but not afebrile.

Subsequently his temperature rose to 104.5° . A third pocketed area was discovered distant from the other two. No viable pneumococci were recovered from the purulent fluid of this area but a precipitin test performed by mixing the specimen of exudate with Type VIII antipneumococcus serum was strongly positive.

Into the third area 20,000 units of penicillin were injected. Within 48 hours the patient's temperature was normal and his convalescence

to recovery was rapid. X-ray photographs are appended. The last picture was taken four months after discharge from hospital.

Total Number of Intrapleural Injections of Penicillin: Four into the first focus, one into the third focus.

Amount per Dose: 20,000—15,000—20,000—25,000 units into the first pocket; 20,000 units into the third pocket.

Total Amount: 100,000 units.

Result: Pleural exudate of first pocket sterile 24 hours after first treatment. No recurrence of infection in first area but additional pockets were present. Final recovery was complete with limited residual pleural thickening.

Duration of Hospitalization: 62 days after beginning treatment. 15 days after treatment of last localized area of infection.

Case 3. Patient M.B., white, male, age 33 years.

Diagnosis: *Lobar Pneumonia, Empyema. Pneumococcus, Type V.*

The patient was treated for the first five days with sulfadiazine by mouth. Empyema was detected on 2nd hospital day. Local penicillin therapy was instituted on the 3rd hospital day by injecting 40,000 units intrapleurally. No additional treatments were given.

The pleural exudate obtained from each of two pre-treatment taps contained Type V pneumococci. From five subsequent aspirations performed two, six, eight and fifteen days after instillation of penicillin, 200-300 cc. of cloudy material were obtained. No pneumococci were present.

His general condition progressed satisfactorily except for low grade fever which continued for 16 days, together with a moderate leukocytosis, and some night sweats. It is interesting to note that in spite of the inability to demonstrate bacteriologically active infection, the exudate in the pleural cavity continued to accumulate for approximately two weeks before finally disappearing.

Resume: Total number of Intrapleural Injections of Penicillin: One.

Total Amount: 40,000 units.

Result: Pleural exudate sterile 48 hours after local treatment. No relapses. Clinically recovery was complete, but patient was not under observation for a sufficient length of time to observe the final degree of clearing of x-ray shadow.

Duration of Hospitalization after Beginning Treatment: 25 days.

TABLE IV
IRRITATING EFFECT OF PENICILLIN INJECTED INTRAPLEURALLY

| Case No. | Diagnosis | Pleural Fluid W. B. C. | Penicillin Units | 1st Day | | 2nd Day | | 4th Day | | 6th Day | |
|----------|-------------------|------------------------|------------------|----------|-------|---------|--------|---------|------|---------|-------|
| | | | | Cells | Fever | Pain | Cells | Fever | Pain | Cells | Fever |
| 1 | TBC | 590 | 40,000 | Not done | | | 1820 | | | 560 | |
| 2 | Cardiac | 255 | 12,500 | 64,200 | + | + | 36,800 | + | — | 3200 | — |
| 3 | Cardiac | 320 | 10,000 | 17,500 | + | + | 13,500 | + | — | 2920 | — |
| 4 | Cardiac | 620 | 10,000 | 14,500 | + | + | 8900 | — | — | 2750 | — |
| 5 | Cardiac | 180 | 5,000 | 15,500 | + | + | 2190 | — | — | — | — |
| 6 | Pneu. | 210 | 5,000 | 2975 | + | + | | | — | 1225 | + |
| 7 | Alc. Cirv. | 770 | 5,000 | | — | — | 1150 | — | — | | — |
| 8 | Cardiac | 1830 | 5,000 | 5,500 | — | — | | | | | |
| 9 | Cardiac Same as 2 | 340 | Control | 520 | — | — | | | | 540 | — |

The special features of the cases so far described consisted of: 1. The rapidity of sterilization of the empyemal cavity following injection of penicillin; 2. The persistence or probable reaccumulation of purulent exudate without demonstrable pneumococci; 3. The somewhat prolonged convalescence with low grade fever; 4. The ultimate recovery.

In considering an explanation of the course, which was characterized in each of the patients by rapid bacteriological "cure" but somewhat delayed clinical resolution, the possibilities which suggested themselves were that a small focus of undetected living organisms remained under the fibrin coating of the pleura even though aspirated material was sterile, or that the decomposition of the sterile pus produced toxic substances acting as irritants, or that the penicillin was itself irritating locally.

The latter possibility lent itself readily to testing. Accordingly, solutions containing from 5,000 to 40,000 units were injected intrapleurally into eight patients who suffered from hydrothorax due to various causes. The penicillin was introduced after removal of most of the transudate. Subsequent samples of the effusion were obtained on each of the following four to six days and the number of cells per cmm. was determined. The presence or absence of fever or thoracic pain was also noted. The results are contained in Table IV.

In each instance there was a definite but variable rise in the number of cells which was greatest the day after injection and gradually decreased during the ensuing days until a number slightly above the pre-injection level was reached on the 4th to 6th day. Slight fever ($100-101^{\circ}$) and some thoracic pain were present on the day following injection but disappeared within 48 hours.

In view of the evidence of a moderate irritating action of penicillin on the pleural surfaces, the next two patients received smaller doses of penicillin than those employed in the cases already described. The attempt was made to employ a sufficient number of units to obtain the necessary antibacterial effect but to minimize the untoward local reaction. That the dosage employed for that purpose was insufficient is evident from the relapses which occurred in the next two patients.

Case 4. Patient M.L., white, female, age 42 years.

Diagnosis: *Lobar pneumonia, Bacteremia, Empyema. Pneumococcus, Type V.*

X-RAY PHOTOGRAPHS OF CASE 4.

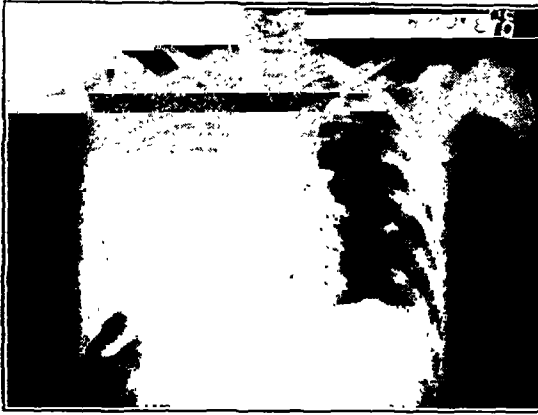


Fig. 5 Before penicillin therapy.



Fig. 6 Two months after leaving hospital.

On admission, treatment for the first three days consisted of penicillin given intravenously. A total of 130,000 units was administered. The bacteriemia cleared within 24 hours. Empyema was demonstrated on the 4th hospital day.

It is interesting to note that penicillin given during the early acute phase of the illness did not in this instance prevent the development of empyema.

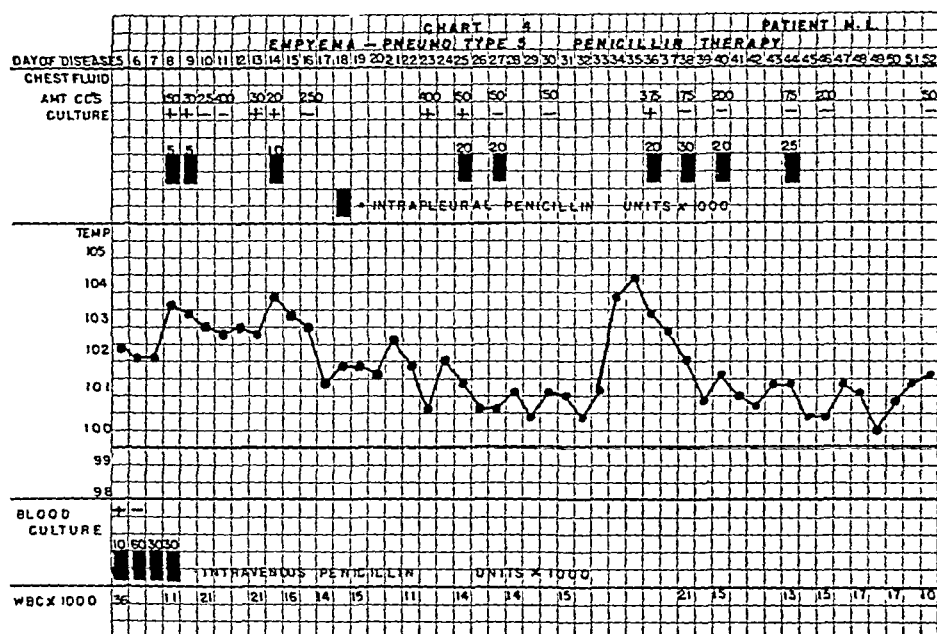
The difficulties in the course of the empyema in Case 4 which were referable to insufficient treatment are illustrated in Chart 4.

From Chart 4 it may be noted that following the injection of 5,000 units, the cavity was not sterilized but that after the second injection of an additional 5,000 units, two aspirations performed 24 and 48 hours later yielded material from which pneumococci were not obtained.

The patient, however, had three subsequent relapses as measured by a return of cultivable pneumococci to the pleural exudate. At each recurrence the dosage of penicillin was gradually increased. The infection was finally overcome by administering four separate doses on alternate days of 20,000-30,000 units.

In spite of her prolonged and irregular course due to inadequate treatment at the beginning, recovery occurred without any greater residue of pleural thickening than that seen in the other cases.

X-ray photographs are appended the last of which was taken two months after discharge from the hospital.



Resume: Total Number of Intrapleural Injections of Penicillin: 9.
Amount per Dose: As indicated in Chart 4 they varied from 5,000 to 30,000 units.

Total Amount: 155,000 units.

Result: Three recurrences of demonstrably viable pneumococci after transient periods of negative cultures. Ultimate recovery was complete with limited pleural thickening.

Duration of Hospitalization after Beginning Treatment: 79 days.

Case 5. Patient M.J., white, male, age 2 years, 3 months, admitted to Pediatric Service of Bellevue Hospital* on 6th day of disease.

Diagnosis: Lobar Pneumonia, Empyema. *Pneumococcus, Type XVI.*

The patient was treated with sulfathiazole and sulfadiazine for the first 12 days of hospitalization without notable improvement. The first successful thoracentesis yielding pus was performed in the 14th hospital day.

The treatment with penicillin in this patient was started by using small doses as in Case 4. The first injection consisted of 5,000 units.

* The patient's record is presented with the permission of Dr. James Wilson, Director of the Pediatric Service.

X-RAY PHOTOGRAPHS OF CASE 6.



Fig. 7 Before penicillin therapy.

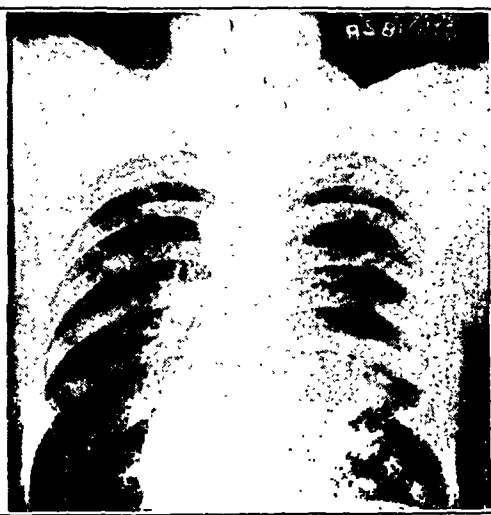


Fig. 8 Four months after leaving hospital.

Two aspirations done one and five days after treatment yielded exudates which were sterile on culture. Viable organisms returned, however, within six days. Additional intrapleural doses of 15,000 and 10,000 units were administered which afforded only transient suppression of cultivable organisms.

Following the second relapse surgical drainage was carried out by rib resection. The patient recovered after a prolonged postoperative convalescence.

Resume: Total Number of Intrapleural Injections of Penicillin: 3.

Amount per Dose: 5,000—10,000—15,000 units.

Total Amount: 30,000 units.

Result: Penicillin therapy unsatisfactory due to insufficient dosage. Surgical drainage required. Recovery was complete.

Duration of Hospitalization: 131 days following thoracotomy.

Case 6. Patient, J.D., white, male, age 58 years.

Diagnosis: Lobar Pneumonia, Empyema, Pneumococcus, Type 1.

The patient was treated with sulfadiazine by mouth for the first eight days of his illness. Empyema was diagnosed on the sixth hospital day. The empyemal strain was found to possess a definite degree of sulfonamide resistance. Following aspiration of the chest on the eighth

hospital day, 25,000 units of penicillin were instilled into the empyemal pocket.

Both of the pre-treatment specimens of pleural exudate were positive on culture for Type I pneumococci. Material aspirated on the day following treatment was sterile. Cultures of all subsequent samples were also negative.

The total amount of treatment given to the patient consisted of three injections of 25,000 units each injected on alternate days.

His clinical course, similar to that of the other patients who did not suffer relapse, was characterized by gradual improvement, but he maintained a slight fever of 99.5 to 100.5° until the 47th hospital day. The delayed absorption of the thick though sterile exudate was particularly striking.

In considering the possibility that the protracted low grade illness might be caused by active undetected infection, intensive therapy was carried out for six days. During the first three days 140,000 units of penicillin were given intravenously and 30,000 units were injected on two occasions intrapleurally. During the remaining three days 20 gms. of sulfadiazine were administered by mouth. No appreciable response occurred.

As an additional measure, when no signs of gradual absorption of the residual exudate could be detected, the site of the pleural pocket was irrigated with physiological salt solution in order to remove as much as possible of the degenerated abacterial pus. Following three irrigations on alternate days the presence of exudate was no longer demonstrable. No effusion reformed and progress to recovery was uneventful.

Resume: Total Number of Intrapleural Injections of Penicillin: 3.

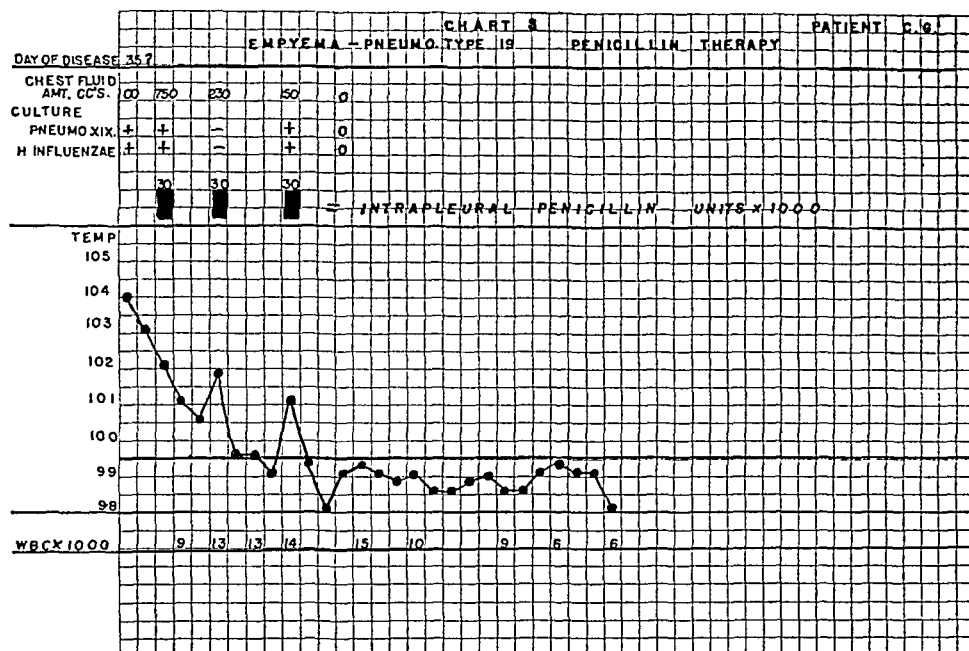
Amount per Dose: 25,000 units.

Total Amount: 75,000 units.

(The amounts given above do not include the late period of additional therapy since the latter treatment did not influence the abacterial pus.)

Result: Pleural exudate sterile 24 hours after first treatment. No relapses. Recovery was complete with residual thickening of pleura.

Duration of Hospitalization after Beginning Treatment: 51 days.



Case 7. Patient C.G., white, female, age 27 years.

Diagnosis: Pneumonia, Pneumopyothorax. Pneumococcus, Type XIX, Hemophilus Influenzae.

The patient had been ill six weeks before admission with a disease which began as an upper respiratory infection. Her local physician had tapped her chest on one occasion and obtained fluid. When her condition remained unchanged she was admitted to the hospital suspected of having tuberculosis. Her course is illustrated in Chart 5.

On admission x-ray examination revealed the presence of both an effusion and air in the right pleural cavity; 100 cc. of thick purulent exudate were removed by thoracentesis. Pneumococcus, Type XIX and Hemophilus influenzae were both seen and cultured from the pus.

Following a second aspiration performed two days later, 30,000 units of penicillin were introduced after removal of 750 cc. of infected exudate.

Cultures of material obtained three days later yielded no growth. The suppression of H. influenzae is of interest since Fleming⁴ did not find the strains of H. influenzae which he tested to be susceptible to the antibacterial action of penicillin. It seems likely that the concentration of penicillin introduced into the pleural cavity may have accounted for

X-RAY PHOTOGRAPHS OF CASE 7.

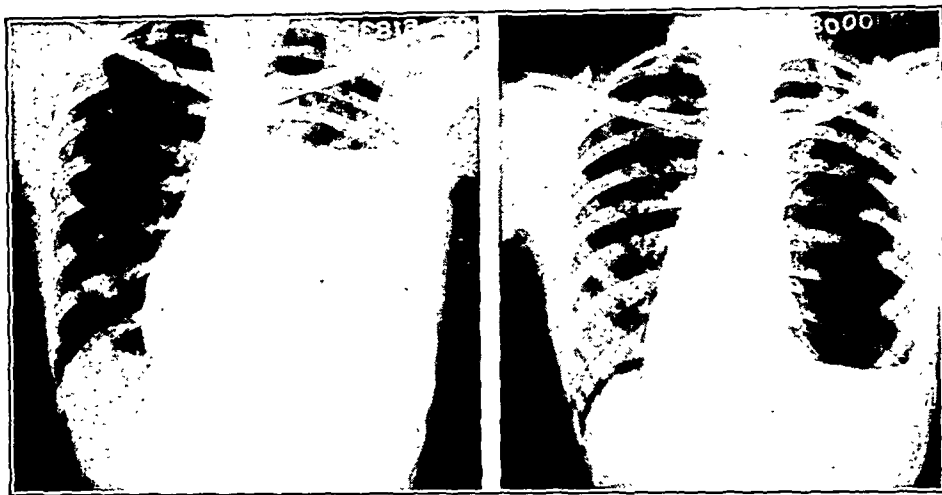


Fig. 9 Before penicillin therapy.

Fig. 10 Two months after leaving hospital.

the effect or that the patient's strain was unusually susceptible to penicillin.

Four days after the second intrapleural treatment, pneumococci and *H. influenzae* were again seen in smears and cultivated from an aspirated sample of exudate. However, after the third instillation of 30,000 units subsequent efforts to obtain fluid were unsuccessful. The patient rapidly improved, her temperature becoming normal 18 days after beginning treatment.

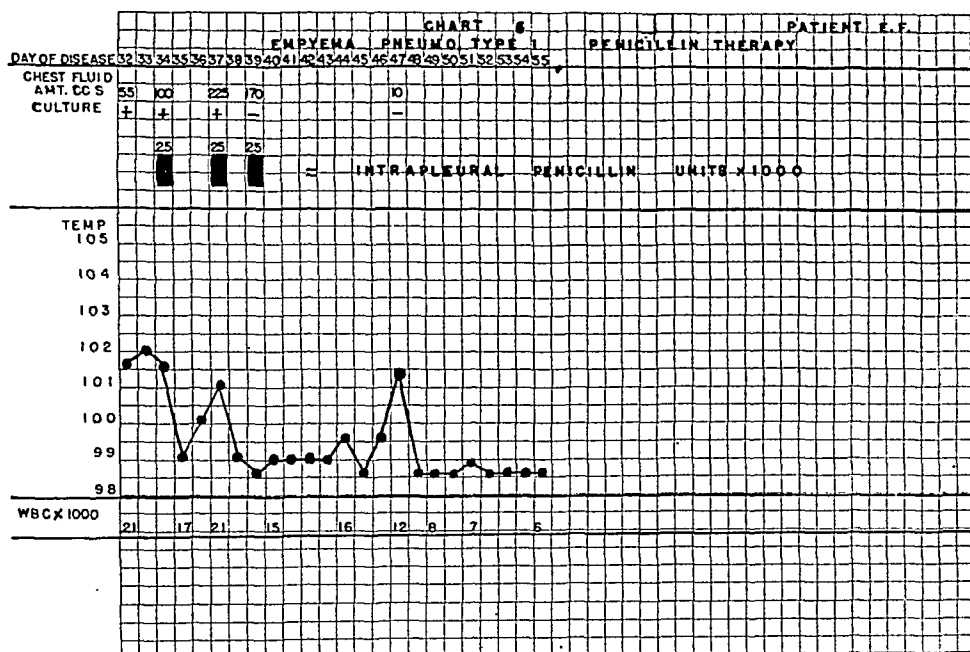
The unusual feature of the course of this patient was the persistence and even increase in the pneumothorax in spite of the rapid disappearance of the pyothorax. Her general clinical improvement paralleled her temperature course as presented in Chart 5. Up to the present time, four months after discharge from the hospital, no signs of effusion have developed in the affected side, but the bronchopleural fistula remains unhealed.

Resume: Total Number of Intrapleural Injections of Penicillin: 3

Amount per Dose: 30,000 units.

Total Amount: 90,000 units.

Result: One bacteriological relapse following second treatment. The pyothorax together with clinical and laboratory signs of infection disappeared but pneumothorax persisted.



Duration of Hospitalization Following Beginning of Treatment: 26 days.

Case 8. Patient E.F., colored, female, age 11 years.*

Diagnosis: Lobar Pneumonia, Empyema. Pneumococcus, Type I.

The patient, treated on the Pediatric Service, received sulfadiazine for the first few days but continued to be ill. Suggestive signs of pleural effusion developed but pus was not obtained until 25 days after admission. Type I pneumococci were present in the exudate.

The course of the illness is represented in Chart 6.

The patient received 25,000 units of penicillin on three occasions, spaced three and two days apart respectively. Cultures of the exudate were sterile after the second treatment. The clinical improvement was rapid, her temperature becoming normal five days after receiving the initial injection of penicillin.

Resume: Number of Intrapleural Injections of Penicillin: 3.

Amount per Dose: 25,000 units.

Total Amount: 75,000 units.

Result: Pleural exudate sterile five days after beginning treatment.

No relapses.

* See Page 156.

X-RAY PHOTOGRAPHS OF CASE 8.



Fig. 11 Before penicillin therapy.

Fig. 12 One week after leaving hospital.

Recovery was complete.

Duration of Hospitalization After Beginning Treatment: 21 days.

DISCUSSION AND OUTLINE OF TREATMENT

It is evident from the results which have been described that penicillin injected locally into the pleural cavity is capable under proper circumstances of effecting a cure in pneumococcal empyema without requiring surgical drainage. In developing the most suitable procedure for administering the drug consideration has been given to the therapeutic requirements with respect to amount of penicillin per dose, the frequency with which the injections should be repeated, and the number of repetitions that may be necessary. Although no arbitrary standards may be set at the present time, the favorable results so far obtained constitute a basis for formulating the details of treatment.

Amount of Penicillin, per dose, for Intrapleural Injection. In the two cases which received 5,000 to 10,000 units, pneumococci disappeared temporarily from the pleural exudate as determined by microscopic examination and culture of the specimens but relapses occurred in both instances.

When larger doses ranging from 25,000 to 40,000 units were employed, in only one instance did a relapse occur (Case 7), and even in

that case the infection was subsequently eliminated following one additional dose.

On the basis of present experience, therefore, 30,000 to 40,000 units appears to be an adequate amount per dose.

Frequency of Injections. The preliminary studies mentioned earlier in this article indicated that the activity of penicillin is retained for at least 48 hours to 72 hours after injection into an empyemal pocket. The fibrinous exudate appears to retard absorption but does not destroy the antibacterial quality at a rapid rate.

Furthermore, the tests carried out with repeated samples of exudate have shown that the initial suppression of the organisms that follows treatment is maintained for at least two to three days.

On the basis of these findings, therefore, no demonstrable advantage seems to be gained by performing thoracentesis oftener than every other day.

Number of Repeated Injections. Even though Case 2 recovered following a single injection of 40,000 units, and Case 1 received only two injections of 40,000 units each, treatment in the other patients was extended to at least three separate injections. In view of the fact that the end point of active infection is liable to be obscured by the persistence of low grade fever and the delayed absorption of the exudate even though sterile, the determination of the time at which treatment may be stopped has not been clearly defined. On the basis of practical experience, however, when clinical improvement appears to be progressive and the exudate remains sterile, three separate injections may, in most instances, be sufficient.

PLAN OF TREATMENT

Thirty to forty thousand units of penicillin contained in 30 to 50 cc. of isotonic salt solution injected intrapleurally on alternate days for at least three doses.

As a further measure in hastening recovery it is desirable at the time of bedside aspiration to irrigate the cavity with a few hundred cc. of physiological salt solution before introducing the penicillin and to repeat the procedure, if necessary, at intervals of several days after treatment is stopped in order to hasten the removal of the degenerated sterile exudate and minimize the reaccumulation of an effusion.

SUMMARY

I. *Lobar Pneumonia*. Penicillin has been found to be highly effective in the treatment of pneumococcal pneumonia.

Of 46 treated patients, 3 (6.5 per cent) died and 39 recovered in a striking manner indicating the special value of the drug. The response was not clearly defined in 4 patients, one of whom probably had primary atypical pneumonia and the other 3 had unrelated underlying pulmonary diseases which prolonged their illness beyond the usual course of pneumonic resolution.

Bacteriemia, which occurred in 14 of the patients, disappeared in every instance following injections of penicillin.

On the basis of quantitative data presented and discussed in this article, a tentative regime for the treatment of pneumonia with penicillin is outlined.

Factors relating to the relative values of penicillin and sulfadiazine in the treatment of pneumonia are discussed.

II. *Pneumococcal Empyema*. Eight patients with pneumococcal empyema have been treated by intrapleural injections of penicillin.

In seven, the infection was eliminated by the local therapy without requiring surgical drainage. Six of them recovered completely with only a restricted area of pleural thickening remaining as a permanent alteration.

In one patient, who had pyopneumothorax on admission, the pyothorax cleared up satisfactorily but the pneumothorax arising from a bronchopleural fistula which was present before treatment was begun, has persisted.

In another patient, who was insufficiently treated at the beginning with penicillin, relapse occurred and surgical drainage was instituted.

Following discharge from the hospital, the patients have returned for reëxamination at varying periods, after one week for one patient, and from 4 to 6 months for the others. With the exception of the case with pneumothorax, the others have remained well and free of symptoms.

Strains of pneumococci derived from the empyemal pus of patients whose pneumonia had been previously treated with sulfadiazine were found to possess varying but definite degrees of sulfonamide-resistance.

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A CRITICAL REVIEW OF GASTROSCOPY*

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IT is now over ten years since gastroscopy by means of a flexible gastroscope was first introduced in this country at the Massachusetts General Hospital.¹ It, therefore, seems appropriate to make a decennial report on the present status of gastroscopy. During this period we have made 1600 gastroscopic examinations, or an average of only about three per week. I believe this indicates that the hospital staff is still not fully aware of the value of the procedure, nor the ease with which it can be performed. This is unfortunate, but must be expected with any new method of examination. On the other hand, the relatively small number of cases examined shows that we are not making it a routine method of study, and I believe this is fortunate since special studies should be undertaken for specific indications.

INSTRUMENT

In 1932 Rudolf Schindler, a German physician, collaborated with George Wolf, an optical physicist, to produce the Wolf-Schindler flexible gastroscope.² There are fifty-one elements in the optical system. Each lens is of short focal length and conveys the image to the next lens, so even when the flexible portion is curved it is still possible to see through it. The great flexibility of the lower part facilitates, as well as safeguards its passage through the esophagus into the stomach. The history of gastroscopy prior to 1932 deals with rigid instruments of various shapes and sizes, all of which were finally discarded as being too unsafe for practical use. The safety of the present instrument is attested by the fact that only one death occurred in over 22,000 examinations by sixty gastroscopists (0.004 per cent). Two modifications of the flexible gastroscope (Fig. 1) are worthy of mention: (1) The omniangle feature developed by Cameron which enables the operator to increase the range

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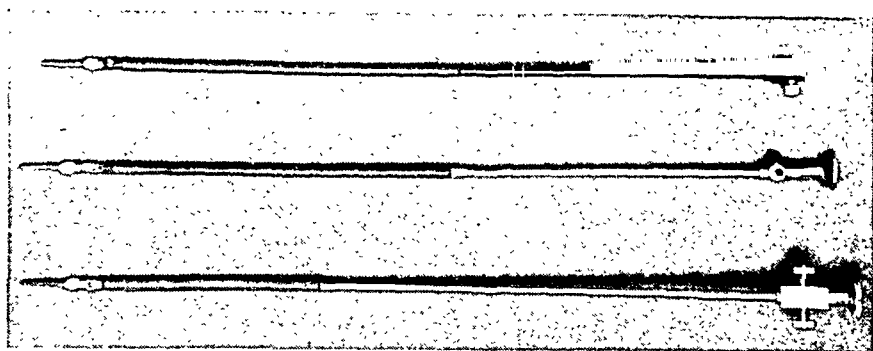


Fig. 1. Wolf-Schindler flexible gastroscope; Cameron omniangle flexible gastroscope showing mirror at distal end, angle of which is controlled by electromagnet; Taylor flexible gastroscope showing ratchet handle for controlling the flexible portion.

of vision by changing the angle of the mirror at the distal end. This is accomplished by an electromagnet controlled by a switch at the proximal end. Although this makes the instrument slightly more difficult to pass, I believe the better view obtained more than justifies its use. (2) The Taylor gastroscope,³ the flexible part of which can be curled up or allowed to lie flaccid. It is flexible in all directions, but can be bent forward and backward in the plane of the objective up to the limits of optical flexibility. This control is obtained by a mechanical device manipulated from the proximal end of the instrument. By reason of this controllable flexibility, Taylor claims the following advantages: "Greater safety of instrumentation, less likelihood of failure of instrumentation, abolition of blind areas in the stomach, ability to move the instrument about in the stomach so as to inspect any particular area closely at will and from more than one angle and greatly increased illumination with less distortion of the image." On the other hand, Schindler believes that since the Taylor gastroscope has a shorter flexible portion and a longer rigid portion it will be less safe than the Schindler gastroscope because the rigid portion will extend below the cardiac orifice where trauma is likely to occur.

TECHNIQUE

In spite of the fact that in many patients gastroscopy can be satisfactorily performed without preliminary sedation, I believe that medication with nembutal, morphine and atropine tends to allay apprehen-

sion and to provide better relaxation. The most satisfactory anesthesia of the throat is a simple gargle with .4 per cent cocaine or 5 per cent larocaine. The latter is unobtainable at the present time due to the war. Two per cent pontocaine gargle gives satisfactory anesthesia, but reactions have been reported.⁴ Preliminary lavage or drainage of the stomach is necessary only when there is pyloric obstruction; since it takes extra time and is somewhat upsetting to the patient, it is to be avoided if possible. The use of small pillows instead of a head holder is to be recommended because it simplifies the technique, obviates the necessity for a trained assistant, and gives the patient more confidence in firm head support. My feeling is that in all matters of technique the simplest procedures compatible with good results are the best. Using this technique, more than one patient has voluntarily remarked that he would rather have the gastroscope passed than the nasal tube.

INDICATIONS AND CONTRAINDICATIONS

It is imperative for physicians to know when special procedures should be used. The indications for gastroscopy⁵ may be listed as follows: gastritis; unexplained gastrointestinal hemorrhage; so-called "gastric neurosis"; unexplained persistent gastrointestinal symptoms, with negative or inconclusive x-ray examination; gastric ulcer, to determine the appearance and location of the lesion, to differentiate benign from malignant ulcer, and to follow the healing process in benign ulcer; duodenal ulcer, to study the gastric mucosa for the presence of gastritis, gastric erosions or gastric ulcerations; carcinoma, to determine the gross appearance, extent and operability of the lesion; polyposis; the so-called "postoperative stomach"; and occasional cases of suspected foreign body in the stomach. In addition to these indications, we have studied a number of other patients by gastroscopy, including those with pernicious anemia, food allergy, unexplained hematemesis or melena, hiatus hernia, deficiency disease, seasickness, lymphoma, sarcoma, benign tumor and submucosal tumor.

Although in many cases x-ray examination of the stomach may give a positive diagnosis, gastroscopy will often contribute additional information. No stomach which is producing symptoms should be considered normal without gastroscopic study. Gastroscopy bears much the same relationship to gastroenterology as cystoscopy bears to urology.

There are relatively few contraindications to the passage of the gas-

troscope. Esophageal obstruction is the only absolute contraindication. Aortic aneurysm probably should be considered a contraindication. In order to exclude esophageal obstruction it is the policy of the author always to have x-ray examination of the esophagus before gastroscopy. Among the relative contraindications which should be mentioned are esophageal varices, esophageal diverticulum, cardiac decompensation, cervical arthritis and marked debility. Extreme kyphosis or psychoneurosis also may be contraindications. Occasionally patients are so unco-operative that gastroscopy may be very difficult or unwise.

GASTRITIS

Gastritis is the commonest disease of the stomach. Everyone agrees that the best method of diagnosis is by gastroscopy. A positive x-ray diagnosis of gastritis when made by an observer experienced in the relief technique is usually of some significance, but should be checked by gastroscopy for the following reasons: (1) To determine whether or not gastritis is really present, for occasionally the enlarged rugae and other roentgen criteria in the diagnosis of gastritis seem to be of little or no significance; (2) to study the type, degree, location and extent of the gastritis if present; (3) to note the presence or absence of erosions or superficial ulcerations; (4) to demonstrate additional pathology, as, for example, a gastric ulcer not seen by x-ray; and (5) to help differentiate hypertrophic gastritis from carcinoma, sometimes an impossible differential diagnosis even with all methods of examination.

Acute or superficial gastritis is a disease usually of relatively short duration characterized by no typical symptomatology, but often accompanied by vague epigastric pain or distress, sometimes gas, nausea, vomiting and anorexia. Alcoholic gastritis is usually of the acute superficial variety, but Gray and Schindler⁶ observed that the stomachs of 55 per cent of chronic alcoholics were essentially normal, the remaining 45 per cent showing mainly superficial gastritis, atrophic gastritis or a combination of the two. No method of diagnosis is reliable except gastroscopy. The gastroscopic picture is characterized by reddening of the mucosa, edema, and adherent secretion.

Chronic or hypertrophic gastritis often very closely simulates peptic ulcer in symptomatology. In a study of 117 cases of hypertrophic gastritis occurring without other gastric or duodenal pathology, Benedict⁷ found the commonest symptom was epigastric pain, which occurred in

74 per cent of the cases. It was relieved by food or soda in 81 per cent, related to meals in 52 per cent and present at night in 21 per cent. Other frequent symptoms were vomiting (45 per cent), hemorrhage (42 per cent), gas (41 per cent), sour eructations (16 per cent) and heartburn (15 per cent). Clinical improvement was in most cases definitely correlated with the improvement in the gastric mucosa as seen by gastroscopy.

Atrophic gastritis, perhaps better called gastric atrophy, may occur as an independent disease characterized by vague indigestion, anorexia, weakness and anacidity, but the diagnosis is more commonly made when it occurs in association with pernicious anemia. In either case, the gastroscopic picture is unmistakable, the gastric mucosa exhibiting a smooth pale, grayish yellow or grayish green appearance with a network of blood vessels easily visible shining through the thin layers of the stomach wall. The probability that tumors of the stomach arise from an already diseased mucosa and the fact that they occur more commonly in an atrophic mucosa makes the diagnosis of gastric atrophy an important one from the standpoint of carcinoma.

Postoperative gastritis has been put in a class by itself by some observers, but I do not see how it can be so considered. Most stomachs that have been operated upon have been the site of ulcer or cancer and all ulcers and cancers are accompanied by some gastritis. The fact that a certain amount of gastritis persists after gastrojejunostomy or resection is to be expected. It is usually of the superficial or hypertrophic variety, or a combination of both.

Hemorrhage is a very important finding in gastritis and may occur in any type of gastritis with any degree of severity. In a study of 42 cases of bleeding from gastritis⁸ I found 13 cases had bled from the superficial variety, 12 hypertrophic, 2 atrophic, 5 postoperative and 10 mixed. There had been 7 mild, 14 moderate, and 21 severe hemorrhages. X-ray examination was negative in 33 of the 42 cases. Erosions, superficial ulcerations and an edematous hyperemic friable mucosa with generalized oozing were the sources of the bleeding.

There is no specific treatment for superficial or hypertrophic gastritis. The superficial or acute variety usually responds fairly readily to the usual dietary measures with elimination of alcohol, limitation of tobacco, and dental attention. Sixty-three per cent of the cases of hypertrophic gastritis recently studied were relieved by bland diet with or

without alkali, belladonna, hydrochloric acid, etc. All cases of gastric atrophy respond to peroral or intramuscular liver therapy,⁹ only a few respond poorly, the majority being entirely relieved. The gastroscopic appearance of the mucosa may be very much improved following adequate liver therapy.

The correlation of gastroscopic and pathological findings in gastritis¹⁰ has been shown to be fairly accurate. Superficial gastritis as described by the gastroscopist corresponds to the acute exudative gastritis of the pathologist. The term atrophic gastritis is used by both gastroscopist and pathologist to denote the same type of mucosa. Hypertrophic gastritis as described gastroscopically corresponds to an exaggerated form of the physiological plasma cell and lymphocytic infiltration of the normal stomach. In the series of 51 cases of all types of gastritis carefully studied there was complete or partial gastroscopic-pathological agreement in 88 per cent.

ULCER

In the study of gastric ulcer gastroscopy may reveal an ulcer not previously proven, may demonstrate multiple ulcers in a patient suspected of having only one lesion, may indicate that a severe gastritis accompanies the ulcer, and may be of assistance in differentiating a benign from a malignant lesion.

Walters and Clagett¹¹ have recently pointed out that although the accuracy of roentgenologic diagnosis of lesions of the stomach is remarkably high, there is always the chance that a small lesion or one situated high in the stomach may be overlooked. Gastroscopy should always be considered in a patient in whom there is a suggestion of a gastric lesion even though the roentgenologic examination does not reveal any abnormality. We know that erosions and superficial ulcerations frequently accompany gastritis and that such lesions are usually demonstrable only by gastroscopy. They indicate an inflammatory process with destruction of the mucosa and are, therefore, real ulcers even though there may be a difference of opinion as to whether or not they are true peptic ulcers. At any rate, there is no doubt that such erosions and superficial ulcerations may be the cause of symptoms and, therefore, the knowledge of their presence is of great importance. The fact that such lesions do not always cause symptoms is no reason to discredit their significance for a large peptic ulcer may be present without giving rise

to symptoms. The demonstration of more than one ulcer or of a severe gastritis accompanying an ulcer may alter the course of medical or surgical treatment, for a knowledge of the location and appearance of the ulcer or ulcers, and information as to the localization and severity of the gastritis will influence one's decision as to the medical regimen or the optimum time for surgery.

The differentiation of benign from malignant lesions of the stomach may be difficult or impossible. Templeton and Boyer¹² have pointed out, however, that inasmuch as no one method of examination is infallible, the use of all clinical, laboratory, roentgenologic and gastroscopic methods together is more likely to lead to a correct diagnosis. Each examination supplements the other and the wise physician will study the patient as a whole. When the roentgenologist is doubtful, the gastroscopist may be reasonably certain and vice versa. In a recent case the roentgenologist saw a lesion in the antrum, but was doubtful as to its nature. A gastroscopy was requested which showed a sloughing nodular ulcerating lesion obviously malignant (later proven at operation). In other cases the ulcer seen by gastroscopy may look benign, but x-ray may show so much rigidity that malignancy is almost a certainty. Usually an ulcer which appears to have sharp margins and a clean gray base is benign and an ulcer with slightly ragged, irregular or nodular margins and a dirty base is malignant. There will be a few cases, however, where all methods of study are doubtful, and unless complete healing takes place within three weeks they should be explored surgically. I believe that no patient should be discharged from the hospital with an unhealed gastric lesion.

Duodenal ulcer cannot be examined by gastroscopy, but the accompanying gastritis which pathologists say is always present can and often should be studied. Occasionally the gastritis is so severe that it is of more importance than the ulcer. I have seen a duodenal ulcer heal completely by x-ray, but symptoms persist or get worse due to severe gastritis. Hemorrhage supposed to have come from a proven duodenal ulcer may in fact have been coming partly or wholly from the gastritis. In a previous paper, 24 cases of gastritis and hemorrhage were discussed in which the question of ulcer was also raised. Since there was no evidence of an active ulcer crater by x-ray in 14 of those cases, the bleeding must have been from the gastritis. A knowledge of the appearance of the gastric mucosa may, therefore, be of importance in duodenal ulcer.

Gastrojejunal ulcer may occasionally be more readily demonstrated

by gastroscopy than by any other method of examination. As a rule, this is true only when the ulcer is on the gastric side of the stoma, for only a small part of the jejunum is visible by gastroscopy even under favorable conditions, and there are times when the stoma may not be seen at all. In doubtful cases gastroscopy should be performed.

NEOPLASM

Carcinoma is the commonest neoplasm of the stomach and when it reaches a certain size the x-ray diagnosis is usually unmistakable. Unfortunately, by that time it may be inoperable. Even more unfortunate is the fact that before that time the patient may not have enough symptoms to consult a doctor, or if he does the doctor may not order an x-ray. Every patient over 35 with indigestion lasting more than a few days should have x-ray examination of his gastrointestinal tract. If such x-ray is negative or doubtful, he should have a gastroscopy. In the early diagnosis of carcinoma, gastroscopy will be of more value as it is used more frequently, but the average clinician accepts a negative x-ray as final and does not request gastroscopy. In the face of persistent symptoms, this is inexcusable, but is due in part to the relative novelty of the method and to the fact that many doctors and patients erroneously consider gastroscopic examination a terrific ordeal. In my experience roentgenologists are more apt to request gastroscopy than clinicians, and they do so whenever they are in doubt about the diagnosis, realizing the limitations of their own method and the supplemental value of gastroscopy. When x-ray examination is difficult due to obesity or high position of the stomach, gastroscopy may be easy and give a correct diagnosis at once. Helpful information as to the appearance, location, and extent of the growth may be added by gastroscopy.¹³

Since it is well known that an atrophic gastric mucosa provides a fertile soil for the development of carcinoma, the diagnosis of gastric atrophy, which can be made only by gastroscopy, assumes an added significance. Whenever this diagnosis is made, the patient should be followed by frequent x-ray and gastroscopic examinations to detect early malignancy. Gastric atrophy occurs not only in association with pernicious anemia, sprue, beriberi, pellagra and other deficiency diseases, but also as an independent entity. Vague indigestion and easy fatigability may point to gastric atrophy. According to Schindler,¹⁴ superficial gastritis may go on to atrophy, which makes the diagnosis of gastritis and

especially the type of gastritis doubly important. In this connection also Hurst has remarked that carcinoma does not develop in a normal healthy gastric mucosa. We must, therefore, know more intimately by direct inspection the appearance of the gastric mucosa in many of our patients.

Other malignant tumors of the stomach are rare and can usually not be differentiated from carcinoma by any method of examination. Doubtful cases should be examined by gastroscopy.

In benign tumors of the stomach, gastroscopic examination is helpful in studying the base of the lesion for the extent of its attachment, and the surface of the lesion for the presence or absence of ulceration. Adenomatous polyps with a broad base tend to become malignant and should, therefore, be removed surgically. Some of the smaller polyps can be seen only by gastroscopy. The differential diagnosis between true polyp and pseudo-polyp can usually be made quite readily by direct inspection, for when the stomach is inflated with air the pseudo-polyps tend to disappear. Submucosal tumors may be observed directly as to size, presence or absence of ulceration, and normal or abnormal peristaltic wave. Two cases recently reported¹⁵ come to mind, in one of which a diagnosis of cancer was changed by gastroscopy to leiomyoma or neurofibroma, later proven and successfully removed surgically; and in the other a stomach apparently normal by x-ray was shown to be the site of a submucosal antral tumor, later proven at operation to be an inoperable carcinoma of the pancreas invading the wall of the stomach.

GASTROSCOPY IN THE ARMED FORCES

In the present war the incidence of gastric disease is notably high. All methods of examining the stomach are, therefore, extremely important. When a soldier complains of digestive symptoms and x-ray study is negative, are we dealing with gastritis or malingering? When a sailor is constantly seasick, can he be used for occasional sea duty on large vessels, must he be kept for shore duty, or has he a really incapacitating gastritis? Gastroscopy is helping us to answer these questions.

GASTROSCOPY AND X-RAY EXAMINATION

These two methods are so entirely different that comparison is not fair. One method supplements the other. X-ray examination should be done first because (1) it is easier, (2) in a given case it may furnish all the required information, and (3) it provides information as to the

normality of the esophagus which the gastroscopist should possess before blindly passing his instrument. In a general way it may be said that x-ray examination is of greater value in the study of gross changes, such as large ulcers and tumors, whereas gastroscopy is superior in the study of the finer mucosal changes as seen in gastritis. In modern medicine both methods are indispensable.

CONCLUSION

Gastroscopy with the flexible gastroscope is an easy and safe procedure, the value of which cannot be doubted. Attention has been called to the omniangle feature and controllable flexibility of certain instruments.

The simpler the technique the better. Four per cent cocaine gargle and small pillows for head support are to be preferred to more complicated methods.

The indications for gastroscopy have been outlined. No stomach which is producing symptoms should be considered normal without gastroscopic study.

The significance of hemorrhage from gastritis has been demonstrated by gastroscopy.

Gastroscopic and pathological findings in gastritis have been correlated.

The usefulness of gastroscopy in gastritis, ulcer and tumor has been critically reviewed.

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THE DIAGNOSIS AND TREATMENT OF PNEUMONIA *

THERE has recently been a large and increasing number of deaths from pneumonia in New York City in spite of the availability of the sulfonamide drugs. Because of this the Pneumonia Advisory Committee to the Department of Health has recommended the release of a statement to the medical profession calling attention to the necessity of early diagnosis and adequate treatment of pneumonia.

In New York City during the past month the number of deaths from primary pneumonia reported to the Department of Health has far exceeded the average number of deaths which would be expected during this period of the year. The number of reported deaths from primary pneumonia is larger than it has been for some years, and is particularly striking since it is occurring in an era when sulfonamide drugs are available. It is also high in comparison with deaths in pneumonia reported in many of the years of the pre-sulfonamide era. This increase was closely associated with the present outbreak of upper respiratory infections which may have contributed to the increase in the number of deaths.

The available evidence on cases of pneumonia in New York City during the present outbreak indicates that the etiology of such cases cannot be related to any particular microorganism and that many different microorganisms are involved. These include pneumococci of various types, the beta-hemolytic streptococcus, *Staphylococcus aureus*, influenza bacillus and Friedländer bacillus.

The intelligent management of the pneumonia patient requires that an etiological diagnosis be established. It has been disappointing to note that since the advent of the sulfonamides there has been a gradually decreasing interest on the part of physicians in determining the bacterial etiology of pneumonia in their patients. The number of bacteriological examinations of sputum performed by the Bureau of Laboratories of the New York City Department of Health has been

* The Pneumonia Technical Advisory Committee to the New York City Department of Health has recommended that this statement be brought to the attention of physicians of New York City.

insignificant in comparison with the number of reported deaths.

In considering the diagnosis and treatment of pneumonia patients, the following points are stressed:

1. There are a number of symptoms occurring in pneumonia which should lead to a suspicion of the presence of that disease and which often help in determining the occurrence of pneumonia in a patient suffering from upper respiratory infection or influenza. These include: (a) Shaking chill, (b) Pleural pain, (c) Rusty or bloody sputum, (d) Continued high fever, (e) Cyanosis, (f) Rising pulse rate, (g) Rising respiratory rate, (h) Shortness of breath, (i) Persistence of fever, accompanied by cough and expectoration, (j) Recurrence of fever following apparent recovery from the initial respiratory disease.

2. A knowledge of the bacterial etiology of the pneumonia is of great value in interpreting the course of the patient's disease, ascertaining reasons for failure of sulfonamide administration, indicating need for other types of therapy and interpreting the occurrence of complications. It is desirable that a bacteriological examination of the sputum, including pneumococcus typings and blood cultures, be performed in all cases of pneumonia as soon as diagnosis is made. Such bacteriological examinations are an absolute necessity when patients do not respond favorably to 18 to 24 hours of adequate sulfonamide therapy. Delaying the bacteriological examination while awaiting results increases the difficulty of ascertaining the etiologic agent.

3. The sulfonamide drugs which are most effective in the treatment of bacterial pneumonia are sulfadiazine, sulfathiazole and sulfamerazine. An accepted dosage schedule for sulfadiazine and sulfathiazole consists of an initial dose by mouth of 4 grams followed by 1 gram every 4 hours until the symptoms have subsided and the temperature has been normal for 48 hours. In the case of sulfamerazine the schedule is similar except for a dosage of 1 gram every 6 to 8 hours instead of every 4 hours. Where patients are seriously ill or in the presence of vomiting, it may be desirable to substitute for the initial oral dose an intravenous dose consisting of 5 grams of the sodium salt of sulfadiazine or sulfathiazole or 4 grams of sodium sulfamerazine dissolved in a liter of physiological saline solution, or in a 5 per cent solution in sterile distilled water. Solutions of these drugs in physiological saline solution may be given subcutaneously in concentrations of 1 per cent or less. Sulfonamide administration should be accompanied by an

adequate fluid intake (3,000-4,000 ml. in an adult) and by the use of alkali sufficient to maintain an alkaline reaction of the urine (6 grams (90 grains) sodium bicarbonate as an initial dose and 2.5 grams (40 grains) of sodium bicarbonate every 4 hours has been recommended as the dosage for adults except when nephritis or other contraindicating disease is present). The primary purpose of such therapy is to maintain a urinary output of at least 1,200-1,500 ml. per day. Great caution must be exercised in the administration of fluids to patients with heart disease or to those who have evidence of congestive cardiac failure. The administration of fluid in these patients must be guided by the urinary output. Fluid administration in such patients should be limited to the minimum amount which will assure such urinary output.

The use of sulfonamide drugs in the treatment of simple upper respiratory infections is undesirable. When the severity of an upper respiratory infection is an indication for sulfonamide administration, investigation for the presence of pneumonia or other complicating disease should be instituted and the drug should be given in therapeutic amounts similar to the schedule indicated above. Small doses of sulfonamides over long intervals may produce drug-fast strains of microorganisms, and may sensitize the patient to the drug. Therefore, small doses of sulfonamides over long intervals are to be avoided.

Patients receiving sulfonamide drugs should be watched for the occurrence of symptoms due to the toxic action of the sulfonamides. These include: (a) Hematuria, oliguria, anuria and flank pain, (b) Skin rashes, (c) Drug fever, (d) Extreme nausea or vomiting, (e) Agranulocytosis.

With the exception of (a) these symptoms usually do not appear until the patient has been receiving the drug for about a week. If sensitivity to one drug becomes apparent, another should be substituted, although sulfamerazine and sulfadiazine should not be substituted for each other.

4. When a patient has been receiving adequate sulfonamide therapy in accordance with a schedule similar to that in (3) and does not respond to such medication within 18 to 24 hours, the patient should be re-evaluated. Such re-evaluation should include a complete physical examination to determine the status of the pneumonia, the presence of complications of the disease and of toxic reactions to sulfonamides; determination of the level of sulfonamide drugs in the blood and an evalu-

ation of the bacteriological findings in sputum and blood. If such re-evaluation indicates that the continued course of the patient's disease is due to pneumonia, and if the sulfonamide level in the blood is low, additional amounts of drug should be given. If the sulfonamide blood level is adequate (5-10 mg. per cent of free drug in the case of sulfadiazine and sulfamerazine and over 3 mg. per cent in the case of sulfathiazole) and if a type-specific pneumococcus (particularly of the common type) has been obtained from the sputum, or if a type-specific pneumococcus has been obtained from the blood culture, type-specific antipneumococcus serum therapy should be begun immediately. Such therapy should be preceded by the taking of a history of allergy and the performance of a skin and a conjunctival sensitivity test. At least 100,000-200,000 units of serum should be administered within 6 hours from the time when serum administration is begun.

5. The availability of specific therapy for pneumonia has not decreased the importance of careful repeated physical examinations of the patient and the many non-specific measures which assist the patient in combating his disease. These include *adequate nursing care*, provision of complete rest, oxygen therapy, maintenance of fluid balance, and the treatment of pleural pain with codeine. Such *treatment is best administered in a hospital*, particularly in the light of the present shortage of nurses. It is recommended that all cases of pneumonia be hospitalized early if hospital facilities are available. It is extremely important that all severe cases be hospitalized.

6. Patients who have had pneumonia for more than a few days and have not responded to adequate treatment should be suspected of having developed complications of the disease. The most important of these is empyema, the diagnosis of which is facilitated by an x-ray examination of the chest as is the spread of pneumonia to previously uninvolved portions of the lungs. Other complications include otitis media, thrombophlebitis, endocarditis and meningitis. The early diagnosis of empyema and its proper treatment may be life-saving.

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RECENT ACCESSIONS TO THE LIBRARY

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- Bates, W. H. *The Bates method for better eyesight without glasses*. N. Y., Holt, [1943], 200 p.
- Blanc Fortacín, J. M. *Fracturas y luxaciones*. Madrid, Morata, 1942, 193 p.
- Calandre, L. *Electrocardiografía*. Barcelona, Salvat, 1942, 122 p.
- Clavero Núñez, A. *Esterilidad matrimonial*. Barcelona, Salvat, 1942, 175 p.
- Compere, E. L. & Banks, S. W. *Pictorial handbook of fracture treatment*. Chic., Year Book Publishers, [1943], 351 p.
- Corona Toledo, L. *Química normal y patológica de la sangre*. 3 ed. Santiago de Chile, Ercilla, 1942, 1132 p.
- Cummins, H. & Midlo, C. *Finger prints, palms and soles*. Phil., Blakiston, [1943], 309 p.
- Dominguez Roldán, F. *Carlos J. Finlay*. La Habana, Cultural, 1942, 382 p.
- Fernández Martínez, F. *Las hemorragias del tubo digestivo*. Barcelona, Salvat, 1942, 113 p.
- Fetterman, J. L. *The mind of the injured man*. Chic., Industrial Medicine Book Co., [1943], 260 p.
- García-Blanco, J. *Manual de química fisiológica, con aplicaciones a la medicina*. Barcelona, Editorial Pubul, 1941-1942, 2v.
- General Electric X-ray Corporation. Technical Service Department. *Medical radiographic technic*. Springfield, Ill., Thomas, 1943, 365 p.
- de Gispert Cruz, I. *Paraplejías espasmódicas*. Madrid, Servet, 1942, 145 p.
- Guirao Gea, M. *Discción reglada de las vísceras del abdomen*. Barcelona, Salvat, 1942, 56 p. 25 pl.
- Heilbrunn, L. V. *An outline of general physiology*. 2. ed. Phil., Saunders, 1943, 748 p.
- de Llamas, L. *Orientación diagnóstica y terapéutica*. Buenos Aires, [Macagno], 1942, 1433 p.
- López Ibor, J. J. *Neurosis de guerra*. Barcelona, Editorial Científico Médica, 1942, 172 p.
- Marie, J. S. F. *English-Spanish, Spanish-English dental vocabulary*. Lancaster, Cattell, [1943], 159 p.
- Mascaró y Porcar, J. M. *Breviario de la urgencia obstétrica*. Barcelona, Salvat, 1942, 150 p.
- Mendez, J. *Evolución y función biológica de las proteínas*. Buenos Aires, Kraft, 1943, 139 p.
- de Moragas, J. *Diagnóstico, clasificación y tratamiento de las oligofrenias*. Madrid, Servet, 1942, 249 p.
- Mosca, C. & Mosca, L. G. *Índice argentino de terapéutica*. Buenos Aires, Editorial Orbis, 1942, 543 p.
- Ockerblad, N. F. & Carlson, H. E. *Urology in general practice*. Chic., Year Book Publishers, [1943], 383 p.
- Papanicolaou, G. N. & Traut, H. F. *Diagnosis of uterine cancer by the vaginal smear*. N. Y., Commonwealth Fund, 1943, 46 p.
- Podolsky, E. *The war on cancer*. N. Y., Reinhold, 1943, 179 p.
- Preston, G. H. *The substance of mental health*. N. Y., Farrar, [1943], 147 p.
- Pryor, (Mrs.) H. (Brenton). *As the child grows*. N. Y., Silver, [1943], 400 p.
- Recasens Serrano, L. *Diagnóstico de la gestación*. Barcelona, Salvat, 1942, 122 p.
- Regan, L. J. *Medical malpractice*. St. Louis, Mosby, 1943, 256 p.
- Ruiz Torres, F. *Resumen de patología interna*. Madrid, [Marsiega], 1942, 454 p.
- Russell, P. F.; Rozeboom, L. E. & Stone, A. *Keys to the anopheline mosquitoes of the world, with notes on their...relation to malaria*. Phil., American Entomological Society, 1943, 152 p.
- Spector, B. *A history of Tufts college medical school*. [Boston, Tufts College Med. School Alumni Assoc., 1943], 414 p.
- Sperling, A. P. *Know your hay fever*. N. Y., Fell, 1943, 241 p.
- Wilkinson, O. *Strabismus*. 2. ed. Boston, Meador, [1943], 369 p.
- Zeno, L. O. *Cirugía plástica*. Buenos Aires, El Ateneo, 1943, 343 p.

PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

JANUARY 6—*The New York Academy of Medicine*. Annual meeting, Scientific program with the Section of Surgery. ¶Executive session—a] Reading of the minutes; b] Presentation of Certificates of Fellowship. ¶Address of the President of the Academy, Arthur F. Chace. ¶Papers of the evening, Use of Plasma and Plasma Substitutes, Including the Treatment of Burns—a] Plasma and plasma substitutes, Robert F. Loeb, Lambert Professor of Medicine, College of Physicians and Surgeons, Columbia University; b] Treatment of burns, Allen O. Whipple, Professor of Surgery, College of Physicians and Surgeons, Columbia University. ¶Report on Election of Fellows.

JANUARY 20—*The Harvey Society in affiliation with The New York Academy of Medicine*. The Fourth Harvey Lecture, "The Anticoagulant from Spoiled Sweet Clover Hay," Karl Paul Link, Professor of Biochemistry, Wisconsin Agricultural Experiment Station.

SECTION MEETINGS

JANUARY 4—*Section of Dermatology and Syphilology*. Paper of the evening—Penicillin in the treatment of syphilis, John F. Mahoney, Senior Surgeon, U. S. Public Health Service; Director, Venereal Disease Research Laboratory, U. S. Marine Hospital. ¶Presentation of cases—a] From the Polyclinic Hospital; b] Miscellaneous cases. ¶General discussion. ¶Reading of the minutes. ¶Executive session.

Section of Surgery—The Section joined with the Annual Meeting of the Academy on January 6, in presentation of its scientific program, and therefore held no meeting on its regular date in January.

JANUARY 11—*Combined Meeting of the New*

York Neurological Society and the Section of Neurology and Psychiatry. Papers of the evening—a] Patients presenting neuro-ophthalmological conditions (Motion pictures), S. P. Goodhart, Montefiore Hospital; b] A case of postencephalitic cyclothymia, Foster Kennedy, Bellevue Hospital; c] A case of platybasia, B. C. Meyer, Mt. Sinai Hospital; d] A case of meningocele treated by destruction of the choroid plexuses (with lantern slides), Tracy J. Putnam, Neurological Institute; e] Demonstration of a defect in synthesis of acetylcholine in patients with myasthenia gravis, Clara Torda, Harold G. Wolff, New York Hospital. ¶Executive Session of the Section.

JANUARY 12—*Section of Historical and Cultural Medicine*. ¶Executive session—a] Reading of the minutes; b] Appointment of Nominating Committee. ¶Paper of the evening, The amenities of medical book collecting, Alfred Hellman. ¶Discussion opened by Eli Moschowitz.

JANUARY 13—*Joint Scientific Session, Section of Pediatrics and Section of Otolaryngology*. Reading of the minutes. ¶Papers of the evening—a] Differential diagnosis and treatment of sinusitis in children, D. E. Staunton Wishart, M. B., Surgeon-in-Chief, Department of Otolaryngology, Hospital for Sick Children, Toronto, Canada (by invitation); Discussion, J. Winston Fowlkes, Oscar M. Schloss; b] The use of sulfonamides in ear infections of children, John D. Kernan. Discussion, Murray H. Bass. ¶General discussion.

JANUARY 17—*Section of Ophthalmology*. Instruction Hour—Recent studies in color vision, Le Grand H. Hardy. ¶Reading of the minutes. ¶Case reports—a] Recurrence of fibrosarcoma of the orbit after seven years (results of radiotherapy), Abraham Kornzweig (by invitation); b] Eye muscle anomalies associ-

ated with aniseikonia—a preliminary report, Miss Edna Knauber (by invitation). ¶ Papers of the evening—a] Diagnosis of simple glaucoma in the preclinical stage by means of pupillography, Otto Lowenstein (by invitation), Mark J. Schoenberg; b] Practical surgical methods in glaucoma, Paul Chandler, Boston (by invitation); c] Diagnostic value of monocular occlusion, Kenneth Roper, Dartmouth Eye Institute (by invitation).

JANUARY 13—*Section of Genito-Urinary Surgery and the New York Urological Society.* Instead of the regular meeting for January 19, the Section held a scientific session with the New York Urological Society at the Yale Club. ¶ Paper of the evening, Studies in urinary calculosis, Linwood B. Keyser, Roanoke, Virginia. ¶ General discussion, Ephriam Schorr, Henry G. Bugbee, Nathaniel P. Rathbun, J. Sturdivant Read.

JANUARY 13—*Section of Otolaryngology.* The regular meeting of the Section was not held on January 19 because it met with the Section of Pediatrics in a joint meeting.

JANUARY 21—*Section of Orthopedic Surgery.* Because of the Annual Meeting of the American Academy of Orthopedic Surgeons in Chicago, no meeting was held of the Orthopedic Section of the Academy.

JANUARY 18—*Section of Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Primary atypical pneumonia in private and general hospital practice, Major Norman Plummer, M.C., A.U.S.; Lt. Herbert K. Ensworth, M.C., A.U.S. (by invitation). Discussion, Russell L. Cecil; b] Clinical studies of immunity to influenza, Thomas Francis, Chairman of the Influenza Commission of the United States Army. Discussion, Colin

M. MacLeod (by invitation). ¶ Executive session.

JANUARY 25—*Section of Obstetrics and Gynecology.* Executive session—Reading of minutes. ¶ Case Report—Extensive varix of vulva and vagina in full-term pregnancy. Delivery by cesarean section. (Lantern slides), Captain Samuel Adler. ¶ Papers of the evening—a] Preliminary report on use of vaginal smear in the diagnosis of malignancy (Lantern slides), Charlotte A. Jones (by invitation) Lieut. Commdr. Locke L. Mackenzie, Theodore Neustaedter; b] Dermatological lesions of the external genitals with special reference to lymphogranuloma (Lantern slides), Arthur W. Grace. ¶ General discussion.

AFFILIATED SOCIETIES

JANUARY 17—*New York Roentgen Society in affiliation with The New York Academy of Medicine.* Papers of the evening—a] The relationship of venography to venous thrombosis and pulmonary embolism, Harold Neuhoef (by invitation), Ernest Sarason (by invitation). Discussion, David C. Bull (by invitation). b] Eosinophilic infiltration of the lungs, Herman Hennell (by invitation). Discussion, Joseph Harkay (by invitation); c] Thoracic manifestations of Boeck's sarcoid, Solon S. Bernstein (by invitation); Marcy L. Sussman. Discussion, Coleman B. Rabin (by invitation). ¶ General discussion. ¶ Executive session.

JANUARY 27—*New York Pathological Society in affiliation with The New York Academy of Medicine.* Papers of the evening—a] Autopsy observations in scleroderma, Margaret Bevans (by invitation); b] Homicide: Its problems for the medical examiner, Milton Helpern. ¶ Executive session.

DEATHS OF FELLOWS

BLODGETT, FRANK JEFFERSON: Sherman Square Hotel, New York City; born in Burlington, Vermont, October 15, 1857; died in New York City, October 30, 1943; received from the University of Vermont the degrees of Ph.B. in 1879 and M.A. in 1885; graduated in medicine from the University of Vermont in 1881; elected a Fellow of the Academy January 2, 1896; and served the Academy as a member of the Committee on Library, 1924-1926, and as its Chairman during 1926, and also as a member of the Council during 1926. He was a member of the State and County Medical Societies.

BULLOWA, JESSE GODFREY MORITZ: 62 West 87 Street, New York City; born in New York City, October 19, 1879; died in this city, November 9, 1943; received his B.A. degree from the College of the City of New York in 1899; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1903; elected a Fellow of the Academy February 7, 1907.

Dr. Bullowa was clinical professor of medicine at New York University College of Medicine; visiting physician to the Harlem and Willard Parker Hospitals; consulting physician to the New York Infirmary for Women and Children and the Norwalk General Hospital, Norwalk, Connecticut; and consulting serologist to the Long Beach Hospital, Long Island. He was a diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, and a member of the American Association of Immunologists, the Society for Experimental Biology and Medicine, and the State and County Medical Societies.

CARR, WALTER LESTER: 112 East 74 Street, New York City; and 66 Congress Street, Greenfield, Massachusetts; born in Lafayette, Jersey City, New Jersey, November 21,

1859; died in Greenfield, Massachusetts, February 2, 1944; graduated in medicine from the Medical Department of New York University in 1882; elected a Fellow of the Academy January 7, 1886; and served the Academy as a member of the Committee on Admissions from 1902 to 1907.

Dr. Carr was consulting pediatrician to the Letchworth Village, Thiells, New York Eye and Ear Infirmary, and Women's Hospital; director of pediatrics at the Midtown Hospital; emeritus clinical professor of pediatrics at New York University College of Medicine; a Fellow of the American Medical Association, a member of the American Pediatric Society, and a member of the State and County Medical Societies.

DOW, EDMUND LEROY: Watch Hill, Rhode Island, and Palm Beach, Florida; born in Baldwinsville, New York, in 1870; died in Palm Beach, Florida, December 1, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1895; elected a Fellow of the Academy April 5, 1900.

Dr. Dow, who practiced medicine in New York for thirty years, retired in 1923. He was at one time a member of the American Association for the Advancement of Science, a member of the American Medical Association and the State and County Medical Societies.

FRISSELL, LEWIS FOX: 135 East 65 Street, New York City; born in Bloomfield, New Jersey, August 2, 1872; died in New York City, October 24, 1943; received from Yale University the degree of B.A. in 1895 and M.A. in 1897; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1900; elected a Fellow of the Academy October 6, 1904; served the Academy as a member of the Committee on Library, 1914-1919; as Recording Secretary, 1937-1939; as Trustee, 1934-1936; and as a member of the Committee on Public Health Relations, 1915-1936.

Dr. Frissell was clinical professor of medicine at the College of Physicians and Surgeons, Columbia University, consultant in medicine to the St. Luke's Hospital, a

Fellow of the American College of Physicians and a member of the State and County Medical Societies.

GEIST, SAMUEL HERBERT: 100 East 74 Street, New York City; born in Brooklyn, New York, July 1, 1885; died in New York City, December 14, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1908; elected a Fellow of the Academy March 5, 1914.

Dr. Geist was attending gynecologist to The Mount Sinai Hospital, clinical professor of gynecology at the College of Physicians and Surgeons, Columbia University, a diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a member of the American Gynecological Society, and a member of the State and County Medical Societies.

KERRISON, PHILIP DAVID: 125 East 72 Street, New York City; born in Charleston, South Carolina, May 19, 1861; died in New York City, January 24, 1944; graduated in medicine from the Medical College of the State of South Carolina in 1895, and New York University College of Medicine in 1898; elected a Fellow of the Academy May 2, 1901.

Dr. Kerrison was consulting aural surgeon to the Manhattan Eye, Ear and Throat Hospital, and the Willard Parker Hospital; a diplomate of the American Board of Otolaryngology; a member of the American Otological Society, Inc., a member of the American Laryngological, Rhinological and Otological Society, and a Fellow of the American College of Surgeons.

KOPP, MARIE ELIZABETH: Ph.D.; 67 Echo Lane, Larchmont, New York; born in Lucerne, Switzerland, August 4, 1888; died in New York City, December 14, 1943; received the degree of Ph.D. from the University of Ferrara, Italy in 1912; elected an Associate Fellow of the Academy January 7, 1937.

LOWE, RUSSELL WALTER: 126 Main Street, Ridgefield, Connecticut; born in Oneida, New York, April 19, 1868; died in Ridgefield,

January 3, 1944; graduated in medicine from the University of the City of New York Medical Department in 1888; elected a Fellow of the Academy March 1, 1894.

Dr. Lowe served as health officer from 1893 until 1939 and was town medical examiner in 1940. He was a Fellow of the American Medical Association and a member of the State and County Medical Societies.

MANGES, MORRIS: 1185 Park Avenue, New York City; born in New York City, May 10, 1865; died in this city January 26, 1944; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1887; elected a Fellow of the Academy February 4, 1892.

Dr. Manges was consulting physician to the Mount Sinai Hospital, a member of the American Association for Thoracic Surgery, a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

MAY, CHARLES HENRY: 70 East 66 Street, New York City; born in Baltimore, Maryland, August 7, 1861; died in New York City, December 7, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1883; elected a Fellow of the Academy November 4, 1886.

Dr. May was consulting ophthalmic surgeon to the Bellevue, French, Mt. Sinai and Monmouth Memorial Hospitals; a diplomate of the American Board of Ophthalmology, a Fellow of the American Medical Association, a Fellow of the American College of Surgeons, and a member of the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, the Association for Research in Ophthalmology, and the State and County Medical Societies.

NUTT, JOHN JOSEPH: 57 West 57 Street, New York City; born in Glencoe, Illinois, June 19, 1870; died in New York City, November 16, 1943; graduated in medicine from New York University College of Medicine in 1897 and Cornell University Medical College in 1899, elected a Fellow

of the Academy December 3, 1908.

Dr. Nutt was consulting orthopedic surgeon and professor of surgery to the New York Polyclinic Medical School and Hospital, consulting orthopedic surgeon to the Nyack Hospital, Long Beach Hospital and Rockland County and Suffern Hospitals, and orthopedic surgeon to the Willard Parker Hospital. He was a diplomate of the American Board of Orthopedic Surgery, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, and a member of the American Academy of Orthopedic Surgeons, the American Orthopaedic Association, and the State and County Medical Societies.

ROBINSON, HORACE EDDY: Pleasantville, New York; born in Portland, Maine, January 16, 1887; died in Pleasantville, January 11, 1944; graduated in medicine from Tufts College Medical School, Boston, in 1912; elected a Fellow of the Academy October 7, 1920.

Dr. Robinson was chief of the division of contagious diseases at Grasslands Hospital, Elmsford; attending pediatrician to the Northern Westchester Hospital, Mount Kisco; a Fellow of the American Medical Association, and a member of the State and County Medical Societies.

ST. GEORGE, ARMIN VON: 773 Park Avenue, New York City; born in Jersey City, March 9, 1892; died in New York City, November 20, 1943; graduated in medicine from the College of Physicians and Surgeons, Columbia University, in 1914; elected a Fellow of the Academy May 4, 1933; and served the Academy as a member of the Committee on Medical Education from 1939 through 1941.

Dr. St. George was assistant director of the pathology laboratories of Bellevue Hospital, consulting pathologist to the Medical Center of Jersey City, visiting physician to the Lenox Hill Hospital, and associate professor of forensic medicine at New York University. He was a diplomate of the

American Board of Pathology, a Fellow of the American Medical Association, and a member of the American Association of Pathologists and Bacteriologists, the American Society of Clinical Pathologists and the State and County Medical Societies.

STENSON, WALTER THOMAS: 45 East 85 Street, New York City; born in Sherbrooke, Ontario, Canada, November 6, 1895; died in Punta Gorda, Florida, December 8, 1943; graduated in medicine from McGill University in 1922; elected a Fellow of the Academy March 1, 1928.

Dr. Stenson was associate attending surgeon to the Lenox Hill Hospital, a Fellow of the American College of Surgeons, a Fellow of the American Medical Association, a diplomate of the American Board of Surgery, and a member of the State and County Medical Societies.

VOGT, ALFRED: Ramistrasse, 73, Zurich, Switzerland; born in Menziken (Aarau) Switzerland, October 31, 1879; died in Zurich, Switzerland, December 10, 1943; graduated in medicine from the University of Zurich; elected an Honorary Fellow of the Academy March 2, 1933.

Dr. Vogt was professor of ophthalmology at the University of Basle from 1918 to 1923 and professor of ophthalmology at the University of Zurich since 1923. He was author of numerous books and textbooks on ophthalmology.

WELT-KAKEIS, SARA: 35 East 61 Street, New York City; born in Austria, December 12, 1860; died in New York City, December 26, 1943; graduated in medicine from the University of Zurich, Switzerland, in 1885; elected a Fellow of the Academy February 1, 1894.

Dr. Welt, who was adjunct pediatrician to the Mount Sinai Hospital, was the first woman pediatrician to serve at that institution, having joined that hospital in 1887. She was a member of the State and County Medical Societies and a Fellow of the American Medical Association.

LECTURES TO THE LAITY

Ninth Series

WAR AND THE EXPANDING FRONTIERS OF MEDICINE



THE Laity Lectures of the New York Academy of Medicine are primarily for the instruction of the public. In so far, however, as they are given by men of eminent authority, who are not only well-informed in their subject matter but also are competent to cast their materials in the language and thought patterns of the laymen, the lectures must prove of singular interest to the physician. In the main, the Laity Lectures illuminate the little appreciated but important fields where medicine broaches upon the other disciplines, and they interpret to the laymen those social utilities of medicine which extend beyond the treatment of the sick individual.

It is both necessary and advantageous to the physician to be informed on these matters. For the time when medicine and its practitioners could be a profession apart, is long past. Today, both the individual layman and the social group look to the physician for, indeed demand of him, instruction and guidance in numerous matters that are in no way concerned with disease. The medical profession collectively and the practitioners individually must be ready to meet these demands, for only thuswise can they fully fulfill their obligations and gain in return the respect and support of the public.

The Laity Lectures series of 1943-44 deals with the large theme of war and the expanding frontiers of medicine. The program of each lecture will be announced in the Folder of the Academy.

Thursday, March 23, 8:15 P.M.

THE PAST, PRESENT AND FUTURE OF CHEMOTHERAPY

COLIN M. MACLEOD, M.D.

Professor of Bacteriology, New York University College of Medicine

The search for chemical substances effective in the treatment of infectious diseases is almost as old as civilization. Earlier attempts, and even those up to the most recent times, have used the method of blind trial and almost innumerable compounds. New direction in the search for even more effective chemotherapeutic agents has risen not only from an understanding of the life processes of micro-organisms, but also from the observations that many organisms in nature produce substances which are inimical to the survival of disease-producing bacteria.

Presiding Chairman Hans T. Clarke, M.D.

BULLETIN OF THE NEW YORK
ACADEMY OF MEDICINE

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Fredrick J. Stare

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



APRIL 1944

THE POSTCHOLECYSTECTOMY
SYNDROME AND ITS TREATMENT*

RALPH COLP

Clinical Professor of Surgery, College of Physicians and Surgeons
Columbia University, New York

REFINEMENTS in the technique of cholecystography have aided substantially in the accurate diagnosis of gallbladder disease. The recent improvements in the pre- and postoperative preparation of patients, together with the standardization of the surgical technique, have so lowered the operative mortality that cholecystectomy is a relatively safe procedure. Unfortunately, the results revealed by follow-up examinations after operation, especially in the group of patients with noncalculous cholecystitis, are far from satisfactory.^{1,2,3,4} The causes of failure following cholecystectomy are many and the complaints which ensue may be bizarre.⁵ Frequently the removal of the gallbladder is followed by acute symptoms identical to those which existed prior to operation. This postoperative symptom complex so characteristic of gallbladder disease is called the postcholecystectomy syndrome.

The postcholecystectomy syndrome may resemble cholecystitis and cholelithiasis in all their varied clinical manifestations and it may simu-

* Presented October 15, 1943 at the Sixteenth Graduate Fortnight of The New York Academy of Medicine. From the Surgical Service of The Mount Sinai Hospital, New York.

TABLE I
END RESULTS OF OPERATION UPON THE GALLBLADDER AND COMMON DUCT

| Condition or Operation | Cases Followed No. | Re-Operation No. | Well No. | Well After One Year No. | Well After Two Years No. | Total Well | | Improved | | Not Improved | |
|--|--------------------|------------------|----------|-------------------------|--------------------------|------------|----------|----------|----------|--------------|----------|
| | | | | | | No. | Per Cent | No. | Per Cent | No. | Per Cent |
| 1. Cholecystectomy for Chronic Cholecystitis with Stones. | 119 | 2 | 70 | 22 | 2 | 94 | 78.9 | 14 | 11.8 | 11 | 9.3 |
| 2. Cholecystectomy for Chronic Cholecystitis without Stones. | 8 | 0 | 2 | 0 | 1 | 3 | 37.5 | 0 | ... | 5 | 62.5 |
| 3. Cholecystostomy for Chronic Cholecystitis with Stones. | 1 | 0 | 1 | 0 | 0 | 1 | 100 | 0 | ... | 0 | ... |
| 4. Cholecystectomy for Acute Cholecystitis with Stones. | 75 | 5 | 48 | 11 | 2 | 61 | 81.3 | 4 | 5.3 | 10 | 13.3 |
| 5. Cholecystostomy for Acute Cholecystitis with Stones. | 7 | 1 | 4 | 1 | 0 | 5 | 71.4 | 1 | 14.3 | 1 | 14.3 |
| Total Operations on Gall-bladder. | 210 | 8 | 125 | 34 | 5 | 164 | 78.1 | 19 | 9.0 | 27 | 12.9 |
| 6. Choledochostomy with Operation on Gallbladder. | 12 | 2 | 6 | 0 | 2 | 8 | 66.7 | 1 | 8.3 | 3 | 25.0 |
| 7. Choledocholithotomy with Operation on Gallbladder | 31 | 7 | 18 | 4 | 3 | 25 | 80.6 | 2 | 6.5 | 4 | 12.9 |
| Total Operations on Gall-bladder and Common Duct. | 43 | 9 | 24 | 4 | 5 | 33 | 76.5 | 3 | 7.2 | 7 | 16.3 |

late many of the physical findings. The acute symptoms sometimes occurring during the convalescent period and most frequently noted during the first two years may be heralded by agonizing colic confined to the upper half of the abdomen, often radiating to either shoulder or the interscapular region. These attacks are commonly accompanied by nausea and vomiting, and are often associated with transient periods of mild jaundice, pruritus, and occasionally intermittent fever and chills. Physical examination may reveal abdominal soreness and occasionally a tinge of icterus.

Hellström,⁶ reporting one thousand and forty-one cases in which cholecystectomy had been done, stated that about 30 per cent of the patients complained of upper abdominal pain and distressing pressure. The symptoms were similar in nature to the colicky attacks described prior to cholecystectomy. In only nine of the cases were the episodes due to residual ductal calculi, and in a few of the patients the attacks terminated in an acute pancreatitis. However, in the majority of cases Hellström offered no explanation which would account for the occurrence of the postcholecystectomy colic.

Doubilet,⁷ in the Surgical Clinic of The Mount Sinai Hospital, personally interviewed two hundred and fifty-three patients following operations for gallbladder disease and saw them at regular intervals during periods varying from one to seven years. The end results are summarized in Table I. Practically 40 per cent of all patients who were followed suffered from postoperative symptoms, either temporary or permanent. The majority of this group described the acute episodes as resembling those which had existed prior to operation and in some cases the attacks were frequent and severe enough to require sedation. The pains were of two main types. In the larger group, seventy-eight patients stated that the intense postprandial pain lasted from five minutes to two hours and occasionally radiated to the back. In a smaller group comprising twenty-four patients the pain which lasted from two to twenty-four hours radiated from the left upper quadrant to the shoulders. It was frequently accompanied by persistent abdominal soreness and in two cases an acute pancreatitis developed. In our experience these symptoms might follow the surgical removal of any gallbladder regardless of its pathologic lesions. The postcholecystectomy syndrome was most frequent in those cases characterized by definite colic prior to operation and in which functional disturbances were

demonstrated by cholecystography, but in which surgical exploration revealed the absence of pathologic lesions of the gallbladder or the presence of a noncalculous cholecystitis. It seemed less frequent in cases of calculous cholecystitis. The syndrome was relatively rare when a fibrosed functionless gallbladder and dilated common duct were present.

The etiology of the postcholecystectomy syndrome may usually be attributed to a dyskinesia of the sphincter mechanism. This sphincter spasm may be stimulated either by local causes or by intrabiliary factors such as recurrent or residual calculosis of the cystic or common bile duct, partial traumatic strictures of the choledochus, cholangitis or pancreatitis. In some cases the dyssynergia may be initiated by psychic disturbances or by glandular dyscrasias, and in others it may be the result of a spastic colon. The significance and importance of biliary dyskinesia has been thoroughly reviewed by Ivy, Goldman and Sandblom,^{8,9} Hill,¹⁰ and Bergh and Layne.¹¹ It will only be necessary here to consider certain fundamental anatomic, physiologic and pathologic data which are concerned in the mechanism and production of most cases of postcholecystectomy syndrome. The anatomy of the peripapillary region of the duodenum has been extensively investigated by Letulle and Nathan-Larrier,¹² Giordano and Mann,¹³ and others, and has recently been examined from an embryologic standpoint by Boyden and his associates.^{14, 15} (Fig. 1) The latter have identified longitudinal fasciculi which probably served to erect the papilla and aid in the ejection of bile, a sphincter of the pancreatic duct, a definite sphincter at the terminal end of the choledochus, and in addition a sphincter of the ampulla which was found in about one-sixth of their dissections. The contraction of this muscle, while it prevents the flow of secretions into the duodenum, converts the choledochus and the pancreatic duct into one canal so that bile may pass into the pancreatic duct and pancreatic secretions may pass into the common bile duct. The pathologic significance of this, which is extremely important, will be subsequently discussed. Not only is the sphincter of the common bile duct a distinct anatomic entity, but Bergh¹⁶ has presented evidence to show that it acts independently of the duodenal musculature to which it is intimately connected. However, functionally the sphincter mechanism includes both the intrinsic muscles of the papilla and the associated muscles of the adjacent intestinal wall. It prevents the regurgitation of duodenal contents, aided by the oblique entrance of

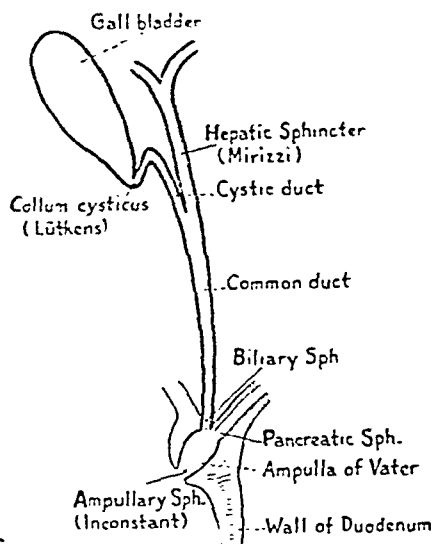


Fig. 1—Location of the sphincters of the biliary and pancreatic ducts.

the choledochus through the wall of the duodenum and by the folds of mucous membrane in the ampulla. The sphincter is most important in its relationship to the physiology of the gallbladder. When the sphincter is contracted between the periods of gastric digestion the normal gallbladder through its absorptive ability and elasticity concentrates and stores large amounts of bile which are continuously being secreted by the liver. The gallbladder acts as a pressure regulating apparatus and insures a continuation of bile secretion by preventing the intraductal pressure in the biliary tree from exceeding the secretory pressure of the liver. The intermittent discharge of bile into the intestine is dependent upon the relaxation of the sphincter mechanism and the simultaneous contraction of the intrinsic musculature of the gallbladder wall according to the Meltzer law of reciprocal innervation. The exact mechanism is not clear and has recently been questioned.¹⁷ However, it is quite understandable that any gradual increase in the tonicity of the sphincter due to reflex causes may cause a stasis of bile, and due to the apparent lack of elasticity of the common bile duct may lead to dilatation of the gallbladder resulting in a hypotonic organ.¹⁸ If, however, the gallbladder musculature responds with increased activity, a hypertonic type of gallbladder may develop. On the other hand, a sudden tonic spasm of the sphincter of Oddi which precipitates a

rapid increase in the intraductal pressure of the common bile duct, or a sudden distention of the gallbladder may cause an acute colic. Lütken's¹⁹ described another sphincter located at the neck of the gallbladder, so-called collum cysticus, as being present in about 75 per cent of his cases. While his original observations were doubted by many, recent cholecystographic evidence affords positive proof of its existence.¹⁰ Sudden spasm of this sphincter may, too, be another cause of gallbladder colic. Recently Mirizzi,²⁰ from cholangiographic studies, has described a physiologic sphincter at the level of the hepatic duct, a spasm of which may cause hepatic pain and transient jaundice. It becomes quite evident that spasm of any of these sphincters may result in an increase of intraductal pressure sufficient in intensity to produce colic. For this reason the removal of the gallbladder, especially the hypostatic, noncalculous type, may give little clinical relief because the original source of the symptomatology may have been a spasm of the sphincter of the common bile duct or the ampulla. In other cases the removal of an apparently innocuous gallbladder together with the cystic duct is occasionally followed by a complete disappearance of the symptoms. The colic may have been due to a reflex spasm of the collum cysticus impeding the free emptying of an actively contracting gallbladder. It is also likely that the normal activity of the sphincter may be simultaneously altered when once acute or chronic pathologic changes in the gallbladder have interfered with its physiologic functions. Clinically it is not unusual to observe jaundice in acute cholecystitis with or without stones and yet at operation to find no organic obstructive cause for the icterus. This transient jaundice is probably due to an obstruction caused by a temporary spasm of the sphincter. Inasmuch as the physiologic activity of the gallbladder and the various sphincter mechanisms are so intimately correlated, cholecystectomy for cholecystitis with or without calculi will invariably be followed by alterations in the sphincter mechanism and in the pathologic physiology of the common bile duct. What these changes are is still a matter of controversy. Some believe that following the removal of the gallbladder the sphincter may lose its tone and the common bile duct may dilate. Puestow²¹ predicates this mainly upon the low intraductal pressure following cholecystectomy and the relief of symptoms produced by operation. This viewpoint has not been generally accepted. Judd and Mann²² have noted dilatation of the common bile duct after cholecys-

tectomy in animals. Colp, Doubilet and Gerber²³ have reported that following section of the sphincter in some cholecystectomized dogs there is a diminution in the caliber of the duct and a reduction in the intraductal pressure. Bergh and Layne,¹¹ McGowan, Butsch and Walters,²⁴ and Doubilet and Colp²⁵ have demonstrated clinically by manometric readings and lipiodol injections of the intubated choledochus that immediate postoperative resistance is offered by the sphincter and that marked spasm may be produced by pharmacologic agents. Moreover, any sudden distention of the intubated choledochus may initiate severe colic. In fact, in some cases reoperated for a calculous obstruction years after cholecystectomy had been performed, an irritable spastic sphincter was suspected because of the high manometric readings obtained from the intubated, dilated and infected choledochus. Definite hypertrophy of the muscles about the ampulla, even to the point of stenosis, has been observed following cholecystectomy by Bergh,¹⁶ Westphal,²⁶ del Valle²⁷ and others. These experimental and clinical observations all tend to support the existence of spasm of the sphincter of Oddi and lend support to the current concept that biliary dyskinesia is an instrumental factor, not only in the causation of gallbladder disease, but in the production of the acute and uncertain symptomatology subsequent to cholecystectomy. The fact that many patients gain eventual relief and few suffer severely from the postcholecystectomy syndrome may be explained in part by the gradual physiologic adaptations of the sphincters and the extra-hepatic bile ducts to the loss of the gallbladder. For, as Ivy has so aptly suggested, there is no reason to assume that the sphincter mechanism reacts the same in all cases; a sphincter which may have been spastic in the immediate postoperative period may lose its spasticity for a time and then regain it later. This may account for the occurrence of colic during convalescence, and its eventual disappearance following appropriate medical treatment. The persistence of the postcholecystectomy syndrome in other cases may be due to dyskinesia of the sphincter of Oddi secondary to intraductal organic disturbances such as recurrent or residual cystic and choledochal calculosis, cholangitis, or stricture formation. But the activity of the sphincter mechanism may cause other complications in the presence of the ampullary sphincter. A contraction of this muscle converts the common bile duct and the duct of Wirsung into one canal so that, depending upon the relative secretory pressure, bile may flow into the

pancreatic duct or pancreatic ferments may mix with bile in the choledochus. The admixture of pancreatic juice with bile in the choledochus is fairly frequent. It may be perfectly innocuous. We²⁵ were able to demonstrate the presence of pancreatic ferments in about 28 per cent of a series of sixty cases in which specimens of bile were obtained from the intubated choledochus. In this particular series the pancreatic reflux was due solely to a spasm of the ampullar sphincter. The pathologic effects of this phenomenon have been proven by the experimental evidence and clinical investigations of Westphal, Popper, Wolfer and others.²⁶ The evidence is now quite clear that pancreatic reflux may cause either a nonperforative bile peritonitis or an acute chemical cholecystitis. In a series of fourteen consecutive cases of acute cholecystitis the gallbladder bile contained pancreatic ferments which probably were the agents responsible for the acute chemical inflammation. It is possible that some cases of chronic cholecystitis and chronic choledochitis with or without stones may be the result of an intermittent pancreatic reflux. It has been appreciated since Opie, in 1906, reported his classic case of a biliary calculus occluding the ampulla that a retrojection of infected bile may cause an edema or an acute pancreatitis. The pathogenesis of this condition has been fully described by Dragstedt and his coworkers.

Dyskinesia of the ampullary sphincter following cholecystectomy may play a significant and important role in the clinical picture of the postcholecystectomy syndrome. Our follow-up studies in those cases in which the presence of a pancreatic reflux was proven have disclosed no clinical evidence upon which changes in the common bile duct could be predicated. Whipple reported three cases of irreparable stricture of the choledochus in which he felt sure that the common bile duct had not been injured at the time of the primary cholecystectomy. When these patients had become deeply jaundiced requiring a second operation nothing was found but a shred of dense connective tissue extending from the duodenum to the portal fissure. He felt that such an extensive destruction of the common bile duct could only be explained by an activated pancreatic reflux. It is barely possible that those cases of chronic choledochitis described by the French surgeons in which the common bile duct resembles a pipe stem, and into which a fine probe could not be introduced, may be due to repeated pancreatic reflux rather than to biliary stagnation.

The effects of postcholecystectomy biliary reflux are known. El-

man²⁹ and others have called attention to recurrent attacks of acute pancreatitis and pancreatic edema following cholecystectomy and have demonstrated an elevation of the blood amylase during the acute phase. It is more than likely that biliary reflux as a result of sphincter spasm accounted for the acute attacks of pain in the left upper quadrant which left a distinct soreness in the twenty-four cholecystectomized patients already described. Two of these cases eventually developed an acute pancreatitis.

The facts which have been presented seem to show that a dyskinesia of the sphincter mechanism contributes materially to the production of certain types of gallbladder disease and acts as a dominant factor in the production of the postcholecystectomy syndrome. The medical treatment therefore in both conditions is essentially the same. It should always be tried before surgery is advised. Little new has been added to the well recognized therapy of biliary colic. It is still customary to give morphine in adequate doses. This gives relief by blocking the higher nerve centers, but it simultaneously increases the muscle spasm of the sphincter mechanism to such a degree that pain often continues when the effect of the opiate has worn off. Small hypodermic doses of morphine may be used as a therapeutic test to substantiate a diagnosis of dyskinesia. It will often cause a tonic spasm of an irritable sphincter with an increase in the intraductal pressure sufficient to cause an attack simulating gallbladder colic. In some of these instances nitroglycerine may afford relief. However, even if this test is positive it does not rule out intraductal pathologic lesions which we have seen may contribute to the picture either of gallbladder disease or the postcholecystectomy syndrome. Antispasmodics such as amylnitrate, glycerol trinitrate, or theophylline, and others should be ideal pharmacologic agents. Unfortunately they are not always successful in relaxing a spastic sphincter. Best and Barr³⁰ feel that although the action of atropine is not constant, it is occasionally effective. They recommend that if a combination of morphine and atropine does not give relief in three hours additional morphine by hypodermic injection and nitroglycerine by mouth should be tried.

Each patient complaining of gallbladder colic should be thoroughly examined in order to determine the factor producing the biliary dyskinesia. It is important to identify and neutralize if possible the precipitating causes. Pavel³¹ has emphasized the importance of the psyche

in the production of biliary dyskinesia. During periods of intense emotional excitement sphincter spasm may become so severe as to produce jaundice and pain. This nervous instability, especially in female patients, is frequently combined with irregularities in menstruation and with symptoms of menopause. In cases such as these, relief has been obtained by the administration of sedatives and proper hormonal therapy. A spastic colon, too, undoubtedly plays a major role in the reflex production of right upper quadrant symptoms. Lahey and Jordan³² have reported that in a series of sixty-five cases, 44 per cent of the patients whose gallbladders could not be visualized with dye showed filling of the organ after a period devoted to the active treatment of their constipation. In the present series of patients, 57 per cent gave a history of constipation prior to operation. Some cases were improved following cholecystectomy but only 37 per cent were cured. The administration of bile salts in adequate amounts, the judicious use of mineral oil and magnesium sulfate and daily enemata of sodium carbonate often lessened the distressing right upper quadrant symptoms. Dyspepsia which was present in 67 per cent of our patients was relieved in 42 per cent of the cases. Efforts were made to ameliorate these distressing symptoms. Measures were prescribed to induce the frequent relaxation of the sphincter and to avoid periods of tonic contraction. Patients were advised to eat bland and non-irritating foods and to take small meals at frequent intervals, for periods of gastric digestion are followed by a discharge of bile into the duodenum. By this simple expedient, biliary stagnation may be prevented. It has also been shown by Doubilet and Colp²⁵ that when hydrochloric acid in high concentration reaches the duodenum the increased acidity intensifies the tonus of the sphincter. Therefore, if a test meal disclosed evidences of hyperchlorhydria, anacids were unhesitatingly prescribed to lower gastric acidity in an attempt to diminish sphincter tone. In some cases in which the symptoms of dyskinesia were severe, lavage of the duodenum with magnesium sulfate appeared to relax the sphincter. These therapeutic and dietary measures were found to be effective in relieving the postcholecystectomy syndrome in most patients. In about 8 per cent of the cases the symptoms persisted regardless of treatment. When the attacks became increasingly severe, or were complicated by the presence of biliary obstruction or cholangitis, surgery was advised.

Exploration was usually performed under spinal anesthesia, because

it afforded the most complete muscular relaxation. In these secondary operations it was quite usual to find the omentum, colon, pylorus and duodenum distorted and bound to the under surface of the liver. These firm and dense adhesions may have contributed in part to the symptomatology. The stomach and duodenum were always meticulously examined for the presence of peptic ulcer. The fact that patients have had a cholecystectomy does not eliminate the possibility that an ulcer may have been overlooked or may have developed in the interim. Following the lysis of adhesions the identification of the foramen of Winslow, the stump of the cystic duct, and the choledochus did not present unusual difficulties unless these structures had been partially obliterated by stricture. But any structure which was thought to be the duct was always first aspirated for the presence of bile. The specimen was subsequently examined microscopically, chemically and bacteriologically. The common duct was then opened and carefully probed, especially in its terminal portion, for it is here that impacted stones may be missed. Immediate cholangiography was not practiced. The pancreas, too, was carefully examined. Palpation was often misleading for the organ, while not enlarged, may be the seat of a chronic inflammation as proven by a punch biopsy. The operative findings in this series were found to be calculi in the stump of the cystic duct in two patients, and in the common duct in five patients; evidences of cholangitis were present in two cases and in two others an acute pancreatitis was found. In two patients a stricture of the papilla was encountered, and in seven cases no visible pathologic lesions were found which might account for the episodes of postcholecystectomy colic. The symptoms were therefore attributed to an intractable dyskinesia of the sphincter of Oddi.

Several surgical methods have been advocated to relieve sphincter spasm. Dilatation of the sphincter may be accomplished by passing graduated sounds through the common bile duct into the duodenum. It is a popular but not an entirely innocuous procedure. If the dilatation has been forceful and the sphincter mechanism has been unduly traumatized, an ascending anaerobic infection by *Clostridium welchii* may occur with fatal results. Biliary duodenal intubation has been recommended by Duval³³ and Walzel³⁴ to counteract the spastic sphincter. A T or straight tube is inserted via the common duct and the sphincter into the duodenum. This indwelling tube not only provides for the

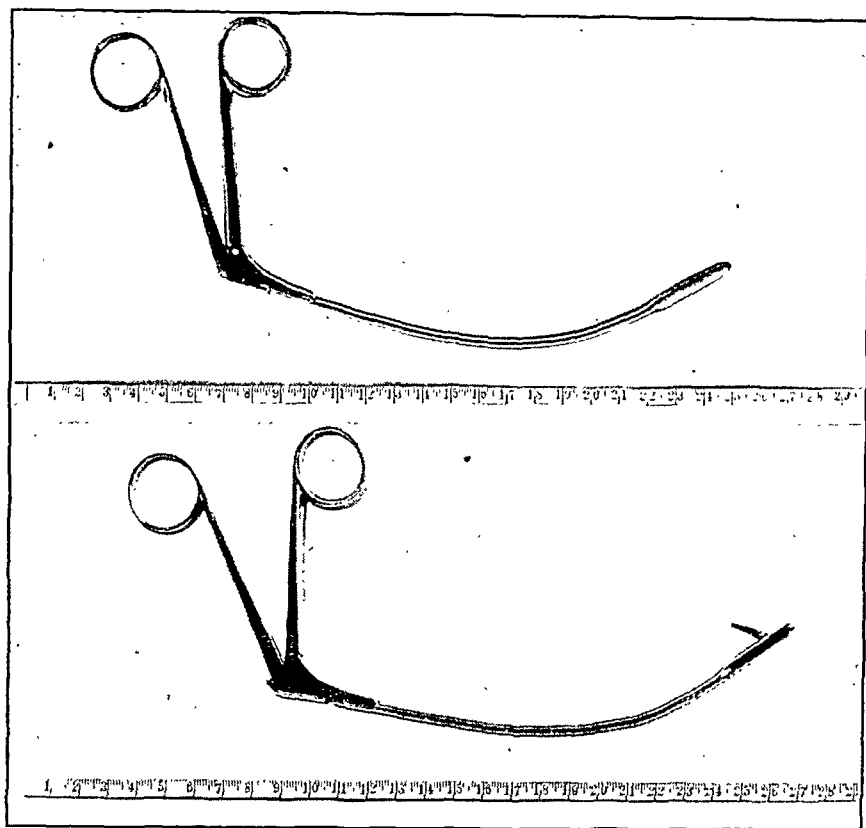


Fig. 2—The sphincterotome, closed and open.

immediate delivery of bile into the intestines but its mechanical presence maintains a continuous dilatation of the sphincter until the T tube is either withdrawn by the surgeon or the straight tube is eventually passed by the patient. Sasse,³⁵ Flörcken³⁶ and Petermann³⁷ have advised choledochoduodenostomy for either an obstructed or a spastic sphincter. An anastomosis between a dilated common bile duct and the contiguous duodenum certainly by-passes the sphincter mechanism. This procedure was proven to be most efficacious in the two cases of papillary stenosis in this series. However, choledochoduodenostomy, in addition to presenting certain technical difficulties, has another disadvantage. Theoretically, with the elimination of the sphincter mechanism there is the possibility of ascending infection by duodenal reflux. In spite of the fact that gastroduodenal roentgenograms in these patients often demonstrate the presence of barium or air in the common bile duct and its radicles, there is very little clinical evidence of cholangitis. The dilata-

tion of the sphincter, either by sounds or biliary duodenal intubation, is temporary and its effects are transitory. A dilated sphincter may eventually regain its tone and recurrent attacks of spasm may ensue. The result of choledochoduodenostomy is undoubtedly more permanent but the operative procedure has an appreciable mortality and a definite postoperative morbidity.

However, there is a direct surgical approach to the spastic sphincter. The sphincter of the common bile duct and sphincter of the ampulla if present may be paralyzed by surgical section of its fibers. This procedure has been done unwittingly since transduodenal choledochostomy was performed for impacted calculi, for it is impossible to extract the stones in these cases without first cutting the musculature of the sphincter mechanism. Archibald³⁸ was one of the first to divide the sphincter transduodenally for a dyskinesia. Del Valle²⁷ sectioned it through the duodenum for Odditis, a condition in which a retracted sphincter partially obstructed the flow of bile. Surgeons have been rather reluctant to deal directly with the sphincter in these unusual cases of intractable dyskinesia. It is quite difficult to identify the biliary papilla after the duodenum has been opened. But the papilla may be easily recognized if a large sized probe has first been introduced through the common bile duct into the region of the papilla. An incision through the anterior duodenal wall may then be made over this area. The sphincter musculature is easily divided under direct vision, following which the duodenostomy may be closed transversely. Recently Strode³⁹ described an effective and successful technique for transduodenal sphincterotomy in two cases of biliary dyskinesia. However, anterior duodenostomy may be followed by peritonitis, duodenal fistula and the physiologic disturbances due to duodenal adhesions. These complications may be obviated by endocholedochal sphincterotomy, a procedure in which the sphincter is divided by a specially designed instrument (Fig. 2) which has been introduced through the common bile duct. The experimental phase of this procedure has been described by Colp, Doubilet and Gerber²³ and the first case in which the operation was performed was reported in 1938.⁴⁰ Briefly, following a choledochostomy the patency of the papilla is first established by the passage of a fair sized probe into the duodenum. The closed sphincterotome is next introduced through the common bile duct and papilla into the duodenum. (Fig. 3). The sphincterotome is then opened, exposing the knife blade. The in-

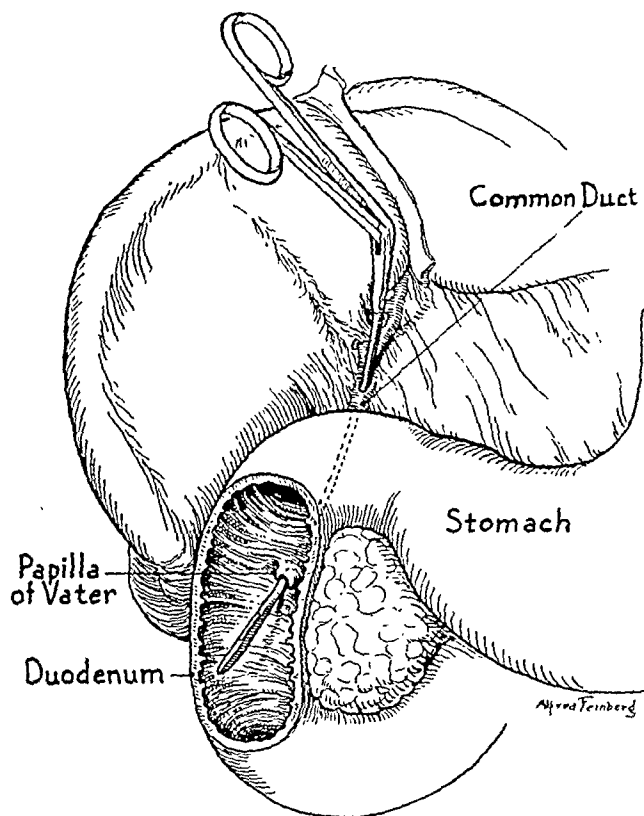


Fig. 3 — The closed sphincterotome is introduced through a cholecystectomy into the duodenum via the papilla of Vater.

strument is carefully withdrawn until the knife blade firmly impinges upon the sphincter. (Fig. 4). As the instrument is closed the knife is driven home, dividing the musculature, after which the sphincterotome may be easily withdrawn. The operation is simple and has not been followed by unusual bleeding. Often, upon opening the instrument, a specimen from the sphincter region may be found in the knife slot. The tissue thus obtained may be examined histologically. The common bile duct is then drained with a T tube. Drainage is important, not only because it provides an exit for bile if postoperative edema should develop in the region of the sphincter, but because it affords an opportunity for manometric readings and lipiodol studies. The drainage of the common bile duct is continued until the closure of the T tube is followed by the absence of pain and the presence of normal temperature. The post-operative course to date has been uneventful and no untoward sequelae developed which could possibly be attributed to the division of the

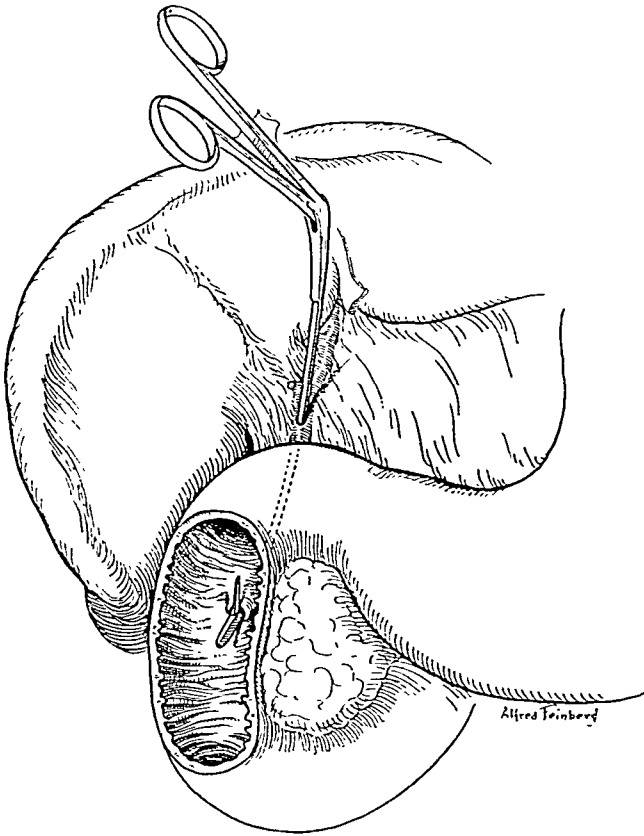


Fig. 4—The sphincterotome is opened and withdrawn until it firmly impinges upon the papilla of Vater.

sphincter. The number of cases in which this procedure has been done is still small. It has been used only in those patients in whom an intractable dyskinesia of the sphincter was apparently the sole cause for the postcholecystectomy syndrome. Its use has not been extended to paralyze an ampullary sphincter in those cases in which either a biliary or pancreatic reflux had been proven. There were seven cases in which endocholedochal sphincterotomy was performed. Six of the cases have been followed, one for six years, one for five years, one for three years, two for eighteen months, and one for six months. All have shown definite improvement and have been relieved of their troublesome symptoms. Whether surgical section of the sphincter permanently destroys its action, and whether the resulting scar will cause a secondary contraction of the papilla with stenosis and biliary stasis, only careful

follow-up of these and other cases will reveal. To date, none of these anticipated theoretical complications have resulted. Many of the other involuntary sphincters of man, when divided, never again fully regain their function, and when healing takes place a stenosis does not result. Perhaps the sphincter of the common bile duct and the ampulla may be placed in a similar category.

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PARENTERAL FLUIDS AND FOOD IN GASTROINTESTINAL DISEASE*

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INTRODUCTION

THE use of parenteral fluids is so extensive at the present time and their value so widely recognized that it would seem superfluous to make it a subject for discussion except that one of my primary purposes is to include this procedure with a relatively new one which may be called the parenteral administration of food, or when the vein is used intravenous alimentation. Indeed, there is no particular reason why all such parenteral injections cannot be considered as food inasmuch as they all introduce nutritional elements and in so doing spare completely any activity on the part of the gastrointestinal tract. More important, however, is the fact that by including all of the nutritional elements in parenteral injections great advances can be made in the treatment of many gastrointestinal diseases.

Adequate parenteral food probably requires but five of the six nutritional elements. The sixth element, fat, is omitted even though there is considerable evidence that it supplies more than calories in the growing organism. It also is a vehicle for vitamins A and D. Nevertheless, for purposes of maintenance during parenteral nutrition for short periods it is probably not essential. The remaining five are the following: 1. Water, 2. Electrolyte, 3. Calories, 4. Protein, and 5. Vitamins.

Of these, the first three are commonly introduced in the usual injections of parenteral fluids, i.e., solutions of Ringer's and saline plus glucose. As to the fifth element, vitamins, many of them have become available in pure form and can be injected either intravenously or subcutaneously. These include vitamin C, thiamine, riboflavin, niacin and several others. However, I might emphasize that any discussion of nu-

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TABLE I

PARENTERAL FLUID AND FOOD: APPROXIMATE REQUIREMENTS AND DEFICITS

| | <i>Normal daily quota</i> | <i>Loss</i> | <i>Total Deficit</i> |
|---|---------------------------|--------------|----------------------|
| Water (in c.c.) | 3,000 | up to 10,000 | 10,000 |
| Electrolyte (as NaCl- in gms.) | 5 to 10 | 20 | 70 |
| Protein (in plasma or as amino-acids- in gms.) | 70 | 200 | 2,000 or more |
| Calories (as glucose- in gms.) | 100* | — | — |
| Vitamins (see text) | — | — | — |

* See text for justification of this figure.

trition whether enteral or parenteral must include consideration of all of the 5 elements listed above because it is quite probable that each requires the presence of the others to achieve adequate utilization. For example, carbohydrate metabolism is known to require the presence of at least thiamine and niacin; utilization of protein undoubtedly requires the presence of glucose; the behavior of protein is influenced by certain of the vitamins. Moreover, fluid and electrolyte balance is often impossible in the presence of severe hypoproteinemia, which commonly accompanies "salt edema." For these and other reasons, therefore, I shall approach the subject of parenteral fluids and food by taking into consideration all of the elements necessary for nutrition. Attention will be confined, however, to the nutritional requirements for maintenance but not for growth, irrespective of whether an adult or a child is under consideration. The reason is obvious; parenteral nutrition is always of limited duration and is used only when the gastrointestinal tract is temporarily out of commission, particularly when an abdominal operation is to be carried out.

Utilization of Parenteral Food: Any fluid or food introduced parenterally obviously reaches the lungs and the systemic tissues before it

reaches the liver, in contrast to absorption from the gastrointestinal tract, from which, of course, they first reach the liver. It is important, therefore, to know whether the parenteral route leads to any significant difference in utilization. The investigations along this line have not been extensive, but there is ample evidence in the case of glucose (provided the injection is not too rapid) that utilization is almost complete and that glycogen of the liver is increased following intravenous injections.¹ The same is true of electrolytes and also of vitamins, although renal excretion of the latter, particularly when given intravenously, does lead to considerable loss in the urine. With protein it has been shown that in the case of appropriate amino-acid mixtures similar results are found with nitrogen balance and serum protein regeneration whether the solution is given intravenously or by mouth.² Moreover, utilization of the protein in plasma transfusions has been demonstrated.³ We may say with confidence, therefore, that the parenteral route permits satisfactory utilization of foods in spite of the fact that they do not first reach the liver.

Indications for Parenteral Food: Parenteral administration of fluids and food is indicated whenever the gastrointestinal tract cannot or should not be used, either completely or partially. Under such conditions failure to utilize the parenteral route will lead to deficiencies in one or more of the five elements listed above.

The first and most obvious indication for parenteral feeding includes patients unable to take any food or fluid by mouth because of vomiting, obstruction, etc. Second are patients in whom the utilization of food by mouth is incomplete or unsatisfactory, as, for example, patients with severe diarrhea or with intestinal fistula. Third are patients in whom oral ingestion of fluids or food is actually deleterious, such as those with peritonitis or other inflammatory disease, or those operated on, in whom complete rest of the gastrointestinal tract is important. Fourth is an ill-defined group in which for one reason or another, usually severe anorexia, the oral intake of fluid or food, while possible, is inadequate. While the intake of food may be increased in these patients by gavage feedings, such a procedure is often followed by vomiting or diarrhea. In this group of patients it may be extremely important to supplement the oral intake by parenteral injections. Fifth, parenteral administration of food may prove important where time is limited for correction of nutritional depletion. For example, in pre-

paring extremely malnourished patients for operation, the parenteral route may enable a nutritional deficit to be corrected even partially in a few days rather than in a few weeks, and this may greatly shorten the length of convalescence.

DAILY REQUIREMENTS VERSUS DEFICITS

The administration of parenteral fluids and food can be most effective only when a sufficient amount is given and retained; moreover, the rapidity of administration is often important. For these reasons it is essential to know rather definitely how much and how rapidly the various elements may be given. In arriving at these figures it is valuable to consider the daily requirements in contrast to the deficits present. Both are important, but the amounts are different with each of the various nutritional elements, which are therefore discussed separately.

Water: The daily requirements for water are, under ordinary conditions, about 3000 cc.; this covers about 2000 cc. in the expired air and perspiration as insensible losses and 1000 cc. to take care of urinary and fecal excretion. In high environmental temperatures the loss in the skin and lungs may reach many liters and this fact obviously increases the daily requirement. Many pathological conditions involving diarrhea and vomiting increase the daily requirement but these will be considered under deficits.

Deficits in water will accumulate whenever the daily requirement is not met by the daily intake. It is increased, of course, by abnormal losses such as diarrhea, vomiting, loss through fistulas, etc. Very rapidly, however, dehydration follows, and unless relieved, it will lead to the death of the individual. Although the exact figures are difficult to obtain, in the most dehydrated individual it is probable that a deficit up to 10,000 cc. may occur and that such a volume may be needed to restore fluid balance to normal. Because about 70 per cent of the body is water⁴ one might expect deficits to be larger. However, the more active fluid compartments of the body comprise but 20 liters⁵ which includes the plasma of the blood and the other interstitial (extracellular) fluid. Of these two compartments, the plasma amounts to but 3 liters. It is probable that not more than half of the extracellular fluid and very little of the intracellular fluid can be lost without serious results. Thus a serious water deficit would scarcely exceed about 10 liters and this should present no problem in correction inasmuch as the par-

enteral administration of this amount of fluid should easily be possible within 48 hours or less.

Electrolyte: There are many aspects of electrolyte behavior which it will be impossible to bring within the scope of this paper, as for example its influence on acid-base balance. However, with normal kidneys one may assume that variations in acid-base relationship produced by electrolyte loss can readily be adjusted by the adequate administration of solutions containing sodium chloride. If there is any reason to suspect that the renal function, even temporarily, is not normal, the compensatory mechanism may not operate and acidosis will remain uncorrected. In such an event it is very important that sodium lactate be substituted for saline or given as lactate-Ringer's solution. This will correct acidosis without action of the kidney and do so much more rapidly. Moreover, the lactate is an added source of glucose to which it is metabolized.⁶ Sodium and potassium abnormalities will not be discussed inasmuch as we shall not be concerned with alterations in capillary or cell wall permeability. The discussion will be confined to the requirements of electrolyte under normal conditions in which sodium chloride or at most the salts present in Ringer's solution are sufficient.

Normally about 5 to 10 grams of sodium chloride are excreted in the urine and unless this is restored an electrolyte deficit will eventually result. Ordinarily, however, the body will first conserve salt in the absence of any intake by excreting very little in the urine. In most cases electrolyte deficiency is associated with water deficiency and the conditions leading to such deficits have already been described. On the other hand, examples of pure electrolyte deficiency occur in at least two conditions without an associated deficiency in water. In one case it is due to excessive perspiration in individuals taking sufficient pure water and is well known as heat cramps or heat exhaustion. The other instance is sometimes spoken of as water intoxication but is extremely rare; in this condition so much water without electrolyte is given that an acute mineral deficiency is produced.⁷ Aside from these two instances, most patients with electrolyte deficiencies are also dehydrated and require water as well as salt.

The magnitude of electrolyte deficits has been well studied by many workers, including especially the well-known investigations of Coller and his associates.⁸ By analyzing the chloride concentration of the plasma of patients who had lost large amounts of water containing

salt (e.g., gastrointestinal secretions by vomiting) they have calculated that for every drop of 100 mg. per cent in serum chloride the patient needs one-half gram of sodium chloride per kg. of body weight. In the case of an adult weighing 70 kg. who shows a drop in the chloride of 200 mg. per cent (a severe deficit), as much as 70 grams of salt would be required for its correction. In terms of physiological saline this would amount to nearly 7 liters. Thus it is obvious that even the correction of such a severe electrolyte deficit is neither difficult nor should it require more than 24 to 48 hours.

Vitamins: Only one of the many vitamins will be discussed because most is known thereof. Vitamin C may be removed from an otherwise complete diet, yet months are required before evidence of scurvy develops. Nevertheless, it is now known that even a severe deficit can be rapidly corrected by the injection of a gram of the vitamin per day for but a few days.⁹ A similar and perhaps just as easy solution probably exists with the other vitamins now available for parenteral administration.

Calories: An adult of average size at rest in bed is said to require 1600 calories per day, which means, of course, that if no calorigenic food is ingested he will obtain these calories from body tissue. The glycogen would be depleted within a day or two, and thereafter calories would originate entirely from protein and fat tissue. Inasmuch as the protein tissue may be considered as essential and the fat tissue as unessential, it is of great importance to determine to what extent we may depend upon fat tissue to supply calories in a patient unable to take any food by mouth. A rough approximation may be obtained from data acquired during the course of complete versus protein starvation. After several days of complete fasting 15 grams of nitrogen appears in the urine,¹⁰ whereas only 5 grams are found when sufficient glucose and fat are supplied to meet the caloric needs. Thus we may assume that the difference of 10 grams represents the amount of protein tissue broken down under conditions of complete starvation to supply glucose for energy requirements. Ten grams of nitrogen represent 62.5 grams of protein or about 250 calories. This means that under complete starvation but one-sixth of the energy requirements are supplied by protein tissue; it may be assumed that the rest is supplied by tissue fat. This is an important calculation inasmuch as it relieves much of the responsibility of supplying full energy requirements in parenteral

injections. If tissue fat may be counted on to supply even three-fourths of the caloric requirements, the problem of administering enough glucose becomes simplified. Thus in an average sized adult 100 grams of glucose per day should be adequate and with the metabolism of enough tissue fat should enable the body to meet the energy requirements without the necessity of using tissue protein.

Protein: Parenteral protein alimentation has been achieved only recently. For a long time no attention was paid to protein intake because it was assumed that such large stores exist that a person could live in health for months or even a year with no protein at all provided merely that his energy needs were met. It is true, of course, that muscle tissue, containing 20 per cent by weight of good protein, forms a large part of the body mass and that it may even be considered as non-essential and therefore a theoretically excellent store of available protein. Moreover, it has been assumed that perhaps a kilogram or two of "deposit" protein is readily available, enough to last for at least several days. The difficulty is that there is no selective depletion of either muscle or "deposit" protein. Much evidence has been accumulated to show that plasma and liver protein as well as muscle is depleted whenever there is an insufficient protein intake.^{11, 12} In other words, we cannot assume that protein intake is unimportant. It may be even more important than water and electrolyte and vitamins. Certainly protein is an essential ingredient of protoplasm and is vital to all life processes.

The daily requirement of protein under normal conditions is fairly well established at about 1 gram per kilogram of body weight. This assumes, of course, the inclusion of enough protein, containing a sufficient proportion of all the essential amino-acids. Such an intake would insure against protein depletion except under certain abnormal circumstances during which excessive amounts of protein tissue are broken down. Fever, trauma, infection cause excessive protein tissue breakdown and may require the daily intake of two or three times the normal amount of protein per day to keep the body in protein, often called nitrogen, balance.

Deficits in protein are most interesting and important inasmuch as they become quite large, are difficult to correct, and require long periods of time, unlike water, electrolyte and vitamin deficits, which are easy to correct. The magnitude of the protein deficit is, of course, increased by the use of protein to supply energy whenever

caloric intake is insufficient. Whereas about 30 grams per day will meet the normal protein tissue breakdown when energy requirements are met, as much as 100 grams may be needed when no energy comes from other food. Moreover, this loss is cumulative. Once protein tissue is lost it cannot be replaced by any other food element. Fat and carbohydrate are both available for energy and the latter is transferable to the former under appropriate circumstances; but except for plants and ruminants, protein requires protein for replacement.

During complete starvation, though adequate water and electrolyte are supplied, a 100 gram loss of protein will in 20 days amount to 2000 grams; in 30 days to 3000 grams. Thus in a severely depleted patient the amount of protein lost will reach a large figure. But the problem becomes greater when one realizes how difficult it is to correct such a deficit rapidly. In the example just cited it would take the patient just as long to correct his depletion as it did to produce it, provided he could ingest 100 grams of protein a day, which in itself may be impossible in the presence of anorexia or other factors preventing or limiting oral feeding. The time factor must also be considered. If one wished to correct a vitamin C deficiency of six months duration in three days one needs only to inject a gram a day of the crystalline vitamin. But can a protein deficit of 2000 grams be corrected in two days by giving 1000 grams a day? This question is merely asked to focus attention on the practical side of meeting severe protein deficits rapidly.

In practice, of course, it is, in all likelihood, not necessary to meet protein deficits completely any more than it is necessary to correct vitamin deficits completely. Nevertheless, the aim should still be to determine how large an intake is possible in order to correct the protein deficit as completely and in as short a time as possible.

AMINO-ACIDS AS PARENTERAL PROTEIN FOOD

The injection of ordinary food protein directly into the blood stream is dangerous in view of the anaphylactic effect of parenterally introduced foreign proteins. An exception to this rule is the apparently relative safety with which solutions of gelatin may be injected intravenously. However, little is known of the metabolic behavior of solutions of gelatin. Moreover, this protein lacks essential amino-acids so that it can scarcely be considered an adequate source of protein food.

At the present time, therefore, human plasma and amino-acid mix-

tures are the only two methods of introducing protein nourishment parenterally. Experience with each of these methods is not very extensive, dating back only about 5 years or so. However, a good deal of information has been accumulated and a few of the pertinent facts may be cited.

Plasma Versus Amino-acids as Parenteral Protein Food: Plasma as a source of protein food has the following *disadvantages*: 1. It is inconvenient and expensive inasmuch as one liter of plasma contains but 60 grams of protein and requires 4 donors besides the processing necessary before it can be used. 2. One liter of citrated plasma contains five grams or more of sodium citrate which under certain circumstances may prove deleterious. 3. It is likely that plasma protein must be metabolized into smaller units before the protein can be utilized by other tissues of the body. 4. It is probable that plasma protein is not a complete protein lacking sufficient arginine and isoleucine.¹³ On the other hand, plasma contains proteins which are apparently utilized by body tissue; however, the great *advantages* of plasma are largely due to the fact that it supplies protein immediately to the circulating blood and thus is of tremendous value in critical cases of hypoproteinemia in which the correction of this deficit is urgently needed.

In contrast to plasma, amino-acids have certain advantages. 1. Amino-acid mixtures as a method of parenteral protein food are much more physiological inasmuch as amino-acids are the form in which protein nourishment normally enters the body. The injection of such mixtures, therefore, is in reality a physiological shortcut, i.e., it supplies protein nutrition without any activity on the part of the gastrointestinal tract whatever. Thus the injection of such mixtures supplies the building stones for the correction of deficits throughout the body. It must be admitted, of course, that synthesis of protein from amino-acids requires appropriate enzymes and hormones and that these may be lacking in certain cases. However, it is probable that when they are present protein synthesis is rapid. 2. Another advantage of amino-acid mixtures over plasma is the relative simplicity and economy with which they may be given; as available at the present time solutions of amino-acids and polypeptides can be injected along with glucose and saline and their cost is not much greater than solutions containing glucose and saline alone.

Protein Hydrolysate as a Source of Amino-acids: While pure crys-

talline amino-acids in appropriate mixtures are available and offer many advantages, the cost of such a preparation is still so great as to make them prohibitive for general use. However, appropriate mixtures of amino-acids and small peptides can be produced by digestion of proteins which have been so purified as to permit their injection with complete safety even in large amounts. The author has used such a preparation which is called Amigen,* an enzymic hydrolysate of casein and pork pancreas and which contains a mixture of amino-acids and peptides in the proportion of 70 to 30. This particular hydrolysate contains all the essential amino-acids as shown by the fact that it supports normal growth in rats when supplied as the only source of nitrogen nourishment.¹⁴ It has also been shown to lead to positive nitrogen balance as well as to satisfactory evidence of serum albumin regeneration both in humans and in animals.^{2, 15}

As available at the present time, Amigen solution is adjusted to a pH of 6.5 by the addition of sodium hydroxide so that each liter of 5 per cent Amigen contains about 5 grams of sodium chloride. Amigen exerts about the same osmotic pressure as an equivalent amount of glucose, its particle size in solution averaging a molecular weight of about 130. As used by the present author a liter of solution containing 50 grams of Amigen and 50 grams of glucose is injected, thus furnishing the patient 4 of the 5 nutritional elements, i.e., 1000 cc. of water, 5 grams of sodium chloride, 50 grams of glucose and 50 grams of protein.

Untoward Reactions: The administration of parenteral protein food in the form of Amigen solution has been fairly extensive and the procedure has passed well beyond the experimental stage. It is probable that thousands of patients have received this form of intravenous feedings; the present author has used it in hundreds of cases. It is true that untoward reactions have been observed following the injection of Amigen solutions, but such a statement can also be made of blood transfusions and in fact of most intravenous injections. The important point is that such injections of Amigen solution have been made in a sufficiently large number of patients to warrant the statement that such a procedure is entirely safe provided the usual precautions are taken for intravenous injections and particularly that the injections be given slowly enough. One liter of 5 per cent Amigen solution contains 50

* Manufactured by the Mead Johnson Company of Evansville, Indiana.

grams of protein nourishment, which is a fairly large protein intake. To introduce such an amount in less than an hour is very apt to provoke nausea, abdominal pain, vomiting, as well as flushing of the skin and a chilly sensation, the nature of which is not entirely understood, although similar reactions have been observed with mixtures of pure crystalline amino-acids made up to match as closely as possible the amino-acid composition of Amigen. From these observations it is fair to infer that such reactions are not due to impurities but are part and parcel of the effect produced by amino-acids themselves when introduced directly into the circulation at too rapid a rate, a phenomenon which probably never occurs under normal absorption from the gastrointestinal tract. In actual practice the speed of injection tolerated without symptoms varies greatly from patient to patient. In coöperative, intelligent individuals the rate of flow is left to the patient himself by placing the regulatory screw clamp within his reach.

True pyrogenic reactions, i.e., chills and fever, have also been observed, but in such instances it has been the experience of the present author that causes other than the amino-acids have been responsible. For example, in the desire to inject Amigen solutions slowly the rate of flow is often cut down so much that the fluid may stop for short periods of time, permitting a reflux of blood into the shank of the needle. Such blood may easily clot and particles of it may enter the circulation when the flow is restarted or increased; under such circumstances, a pyrogenic reaction may readily occur. Contaminated solutions, of course, will obviously produce pyrogenic reactions, and great care must be exerted as with blood and plasma to avoid such contamination. Recently at the Barnes Hospital 200 consecutive liters of 5 per cent Amigen and 5 per cent glucose solution have been injected intravenously into 15 patients with no pyrogenic reactions whatever. In this group the greatest amount given to one patient was 26 liters. Actually our percentage of reactions with Amigen is less than with citrated blood.

Phlebitis: The occurrence of phlebitis following the intravenous injection of Amigen has been observed, but so has phlebitis been encountered with the intravenous injection of other solutions, particularly those which were hypertonic. In the experience of the present author the injection of a solution containing 5 per cent Amigen and 5 per cent glucose produces no more phlebitis than a 10 per cent solution of glucose. It is obvious, of course, that if this solution is diluted with

distilled water the tendency toward phlebitis will be much less. The disadvantage of this, however, is that a larger amount of water is injected than is necessary; conversely, less nourishment can be given from the same volume of fluid.

Subcutaneous Injection of Amigen: The injection of Amigen subcutaneously is preferred by some and the present author has also used this method. It is necessary, of course, to prepare a mixture which is not hypertonic. Ordinarily the dilution of the above mentioned solution containing 5 per cent Amigen and 5 per cent glucose with an equal quantity of pure water permits satisfactory injection of the solution under the skin. At the St. Louis Children's Hospital the subcutaneous solution is prepared by adding equal parts of 10 per cent Amigen, 10 per cent glucose and normal lactate Ringer's solution. Here again the disadvantage of this method of administration is the relatively large volume of fluid which must be given.

CALCULATION OF THE DAILY PARENTERAL DIET

If the patient is clearly dehydrated, it will be necessary at the very outset to inject as much as 5 to 10 liters of normal saline or Ringer's solution to correct the water and electrolyte deficiency. In addition to this, a plasma transfusion of a liter or more may be required to correct an acute hypoproteinemia, particularly when any evidence of circulatory impairment is present or imminent. After these more or less acute requirements have been met, it is probable that the daily amount of parenteral food may be cut down considerably as follows.

For the adult of average weight with a moderate protein deficit, 3 liters of fluid are given each day, of which 1 liter is Amigen solution containing 5 per cent each of Amigen and glucose, the other 2 liters being 5 per cent glucose. Thus in these 3 liters of fluid the patient receives the following nutritional intake:

| | |
|-------------|-----------|
| Water | 3000 cc. |
| Electrolyte | 5 grams |
| Glucose | 150 grams |
| Protein | 50 grams |

The above intake is used ordinarily although in depleted patients one liter of glucose may be replaced by a second liter of Amigen, thus increasing the protein intake from 50 to 100 grams. In more severely

depleted cases, the amount of fluid may be increased to 4000 cc. by the addition of another liter of Amigen and glucose solution. Thus the patient would receive the following:

| | |
|-------------|-----------|
| Water | 4000 cc. |
| Electrolyte | 15 grams |
| Glucose | 200 grams |
| Protein | 150 grams |

In still more severely depleted patients, it may be possible to increase the intake of protein even more in view of evidence indicating¹⁶ that as much as 10 grams of protein per kilo per day can be metabolized. However, clinical experience with the larger amounts of Amigen are still limited; the most the present author has injected has been 300 grams of Amigen and 300 grams of glucose in 24 hours for 3 consecutive days in 2 patients by a continuous venoclysis of 6 liters per day. The injections were well tolerated with evident clinical improvement.

Separately the following parenteral mixture of vitamins may be injected for the daily requirement. Much more will be necessary if a depletion is present or suspected. (The doses listed are approximate and are partly based on the now available preparations which also offer widely variable mixtures. Vitamins C and K, however, are always given individually. Not listed are inositol and choline as well as the fat soluble vitamins which are also available and may be given intravenously, intramuscularly or subcutaneously. Various liver extracts containing vitamins and probably other important elements are also often given parenterally.)

| | |
|------------------|--------------------|
| Vitamin C | 100 mg. |
| Thiamine | 5 mg. |
| Riboflavin | 2 mg. |
| Pantothenic Acid | 4 mg. |
| Pyridoxine | 2 mg. |
| Niacin | 20 mg. |
| Vitamin K | 10 mg. (as needed) |

RESULTS OF PARENTERAL FEEDING IN GASTROINTESTINAL DISEASE

That food is essential for normal resistance to disease should require no proof. Yet it is remarkable how often this fact is overlooked and how frequently we rely on reserves of nutritive elements which

may or may not be present or may have been depleted before operation is carried out. It might be well to cite the striking observations made in this city by Mulholland, Co Tui and their coworkers¹⁷ on the beneficial effects which followed prompt postoperative administration of a large amount of food including protein by utilizing a jejunal tube for alimentation. The important point is that food is just as essential whether the administration can be oral or must be parenteral. Nevertheless, the parenteral administration of food has for decades been confined to water, electrolyte and glucose with the addition of several of the vitamins within the past few years. While correction of dehydration with such fluid has reduced mortality and extended the field of surgery tremendously, still further advances will be made possible by applying knowledge of nutrition, particularly of protein, to parenteral administration in patients unable to take any food by mouth. While the administration of an absolutely complete* parenteral diet has not as yet been achieved, the addition of protein nourishment as amino-acids to parenteral fluid has been of decisive significance. Such a parenteral diet has been given to hundreds of patients and the results have been published by a number of observers.^{15, 18, 19}

Permits Rest Without Starvation in Non-surgical Diseases: In many patients with non-surgical diseases of the gastrointestinal tract, malnutrition is inevitable because a sufficient amount of food cannot be ingested or assimilated. In many instances the physician wishes to put the gastrointestinal tract completely at rest so that this important principle may be utilized. Yet by so doing the malnutrition already present is aggravated. Only by feeding the patient parenterally can the principle of rest be carried out without starvation. Indeed, healing is so dependent on the presence of adequate nutrition that rest of the gastrointestinal tract often defeats its purpose because it increases the degree of malnutrition.

Thus the use of parenteral food in non-surgical diseases is logical and should prove extremely beneficial although few cases have been so treated and the actual results cannot be described. The present author has little occasion to treat such patients, e.g., ulcerative colitis, but he has observed two children in whom a prompt remission of the severe

* Missing is fat and several vitamins. It is not known how serious this is in patients ordinarily treated by parenteral injections. It is probable that for them the elements now available do actually comprise a complete diet. It must be admitted, however, that further research will show the indispensibility of certain elements whose importance is now obscure or unknown.

diarrhea followed complete rest of the gastrointestinal tract (aside from the ingestion of tablets of sulfasuxidine) with the administration of a complete intravenous or subcutaneous diet.

Extends the Indications for Surgery: Extensive gastrointestinal surgery, particularly the removal of carcinoma, imposes a great risk, especially when the patient is malnourished and depleted to begin with. The long and tedious procedures necessary to remove all cancerous tissue has in the past denied many individuals any hope of surgical cure. That adequate preparation before operation will enable much more extensive procedures to be carried out safely is widely known. But such preparation is much more complete when all the elements of the diet, particularly protein, have been included. It has been the experience of the author and of other surgeons as well, that when a patient has received adequate parenteral injections of the 5 nutritional elements described for a week or more, extensive surgical procedures could be more safely carried out with much less tendency toward shock during and immediately after operation. This is particularly true of older patients many of whom suffer various types of malnutrition particularly hypoproteinemia.²⁰

This method of therapy is still relatively new and actual figures of mortality cannot be cited because the amount of experience is not great. It is quite probable, however, that with the use of this new method of preparation the boundaries of gastrointestinal surgery can be greatly increased because much more extensive procedures will become possible with relative safety.

Facilitates Surgical Procedures: Many patients with long-standing diseases of the stomach or intestines particularly those who have had symptoms of obstruction will present at operation an edema of the stomach or intestinal wall which is partly inflammatory but is often partly nutritional. Much of the edema and even distention will subside on complete rest of the gastrointestinal tract as well as efficient gastrointestinal decompression. If to these measures the surgeon will add the administration of an adequate amount of parenteral food the return of the stomach and intestines to a normal healthy condition will be more complete. It has been impressive to note the collapsed thin-walled condition of the gastrointestinal tract in such patients after a week of such preoperative preparation. The technical procedures which have to be carried out are much easier and healing is much more rapid and sure.

Minimizes Postoperative Complications: Here again it should require no detailed evidence to prove that adequate nutrition will enable more perfect and rapid healing. Complications which follow gastrointestinal diseases are to a large measure due to the effects of partial or complete starvation. These inevitable nutritional deficits are aggravated by actual loss from vomiting, diarrhea or exudation from the extensive surfaces of the peritoneal cavity or into the wall of the gastrointestinal tract. Physicians and surgeons alike have not hesitated to put the gastrointestinal tract at rest and have combated the effects of the resultant starvation at least partially by supplying water, electrolyte, glucose and some vitamins. Only recently, however, has the addition of protein made this parenteral diet more complete. Yet it is the protein deficit which is largely responsible for most of the complications. There is an increasing realization that hypoproteinemia, for example, is frequent and associated with many of the difficulties which follow surgery.

An Ounce of Prevention Is Worth a Pound of Cure: After the introduction of amino-acid mixtures several years ago their injection as a means of supplying parenteral protein food was used only in severely depleted individuals who developed difficulties after operation, usually associated with hypoproteinemia. Under these circumstances the protein deficit is great and the correction difficult, requiring many days. On the other hand, if the surgeon realizes that protein deficits are cumulative and inevitable, he will begin to supply protein parenterally from the very moment protein nourishment is withdrawn from the diet; in other words, he will make his parenteral injections fulfill the requirements of a complete diet and thus prevent many clinical manifestations which follow protein starvation. The ~~present~~ author ~~now~~ often includes Amigen solution as routine after any abdominal operation even though the patient is in perfect health at the time of the operation. If glucose is added to the parenteral injections after operation to supply calories, protein nourishment is also added. Indeed, protein is probably more important than calories, inasmuch as the latter can be supplied if necessary from body stores of glycogen, tissue fat and tissue protein. On the other hand, there is no substitute for tissue protein and, unless supplied in the diet as such or as an adequate mixture of amino-acids, depletion is inevitable.

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NUTRITION IN MEDICINE *

The Wesley M. Carpenter Lecture

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NUTRITION is the science of food and its relation to health, and as such it is inseparable from any concept of medicine. Throughout the history and development of medicine, food and nourishment have always been considered as important environmental factors in health, and in the treatment of disease—particularly in convalescence. Current concepts of nutrition are really the result of 20th century developments in chemistry and physiology, and as all of us are aware, the last decade or so has witnessed remarkable advances in nutrition, both in fundamental nutrition and in the application of nutritional information to the diagnosis and treatment of disease and in the broader field of improved health.

This emphasis on relatively recent advances in nutrition does not mean, that as a whole we are today any better fed than we were 100 years ago—for whenever man has consumed food in such variety and quantity that all bodily needs are fully met, he has been well nourished. But these more recent advances in nutrition do permit us to define good nutrition more clearly, and to use available nutritional information more effectively. Unfortunately there have been many overenthusiastic and misleading statements regarding the value of certain nutrients in the treatment of specific diseases, and to health in general. I refer specifically to the vitamin field. There also have been many misleading statements regarding the prevalence of malnutrition in this country. These unsubstantiated claims have had two unfortunate results: they have not encouraged the vast majority of competent medical men to have a real appreciation of good, sound nutrition; and they have opened up a "vitamin racket" rivaling that of the patent medicine days. It is as important that we learn the things that good nutrition cannot do, as it is to learn what it can do.

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The invitation to make this address requested that it include comments on nutritional requirements for man, vitamin therapy, and use and abuse of vitamins in nutrition. After remarks on these points, I wish to comment on recent views concerning the prevalence of malnutrition in this country, and then to mention briefly certain classic experiments which emphasize the importance of superior nutrition to health. Finally, I should like to suggest certain positive measures whereby nutrition may come to be of greater value to medicine.

The nutritional requirements for good health consist of adequate quantities of protein, fat, carbohydrate, certain minerals, certain vitamins, and water. Under ordinary conditions, and even today in this country, the normal individual can obtain adequate amounts of these nutrients from food. In fact, adequate nutrition for man over any length of time can be obtained only by consuming foods in such quantity and variety that nutritional needs are fulfilled. Man relies principally on appetite and on variety in the choice of foods to secure a balanced diet. Variety in the choice of foods is affected by food habits, purchasing power, and availability of food. Probably the simplest principle for the normal individual to follow in attaining good nutrition is to consume a wide variety of foods that have undergone a minimum of processing, and let the appetite be the judge of quantity consumed. One can improve this principle by knowing something of the nutritional requirements of man and how they are fulfilled by various foods, for one can then select those combinations of foods which will furnish in adequate quantity the various ingredients now known to be necessary for good nutrition. But with the ill individual one should not rely on appetite as a stimulus for adequate food intake, for anorexia may be part of the symptom complex.

It is important to remember that there are no absolute requirements known for any food factors. All the requirements we speak of are relative requirements. For example, the amount of protein we need depends in part on the amount of fat and carbohydrate in the diet, the amount of thiamine we need depends on the amount of carbohydrate and fat in the diet, the amount of riboflavin and niacin we need may depend on the amount of protein in the diet, and so forth. There are many complicated and dynamic interrelations in intermediary metabolism, and so when we speak of nutritional requirements we usually refer to an average person on an average diet. The figures given are usually

optimal, as they should be for optimum health, sufficiently high to allow a generous margin of safety for individual differences in requirements, and to cover any errors in our knowledge of nutrition.

Protein is the principal nitrogenous constituent of animal and vegetable tissue. In the process of digestion, the large protein molecules are broken down into units that are simpler from a chemical viewpoint, and ultimately into small molecules, the amino acids. There are about twenty-four known amino acids; of these somewhat less than a half are the so-called essential amino acids. This means only that our body tissues cannot make these amino acids, that we must receive them ready made from our food. The other amino acids play a part in metabolism, but presumably they can be synthesized in the body and hence it is not essential that they be obtained from food. Protein nutrition is thought of today in terms of essential amino acids, but we lack information on the amounts and kinds of amino acids in foods, and on the qualitative and quantitative requirements of man for amino acids, so one still speaks of protein requirement. For the average normal adult, a protein intake of 1 gram per kilogram of body weight per day is sufficient. About one and a half times as much is desirable for the pregnant woman and two or two and a half times as much for the lactating woman or the actively growing child. Most of us obtain protein from both animal and vegetable sources, and generally speaking, those proteins of animal origin which include not only meat but milk, eggs, fish, and fowl are of higher biologic value than vegetable proteins, because they contain more of certain of the essential amino acids. But vegetable proteins supply many of the essential amino acids, and other amino acids, as do animal proteins, which are also used by the body. Some vegetable proteins such as those of yeasts, peanuts, soybeans, and various seed germs are good quality protein.

Thus for the protein allowance, let us use the common figure of 1 gram per kilogram body weight per day, or 70 grams for an average man, and receive some of it from animal and some from vegetable sources. One cannot be too dogmatic about the proportions of animal and vegetable protein, nor about the absolute amount of protein. Recent investigations¹ with man have shown that as little as 50 grams of protein, of which not more than 5 grams were animal protein, were sufficient to maintain good health in hard working, healthy young adults over a two month period. But may I emphasize that the diet used in

these investigations was excellent in all other nutrients and provided adequate calories, and that 50 or 70 grams of protein is not the same as 50 or 70 grams of protein food. In terms of protein foods these values would be three to five times more because of the water content of the food. May I further stress that these subjects were healthy young adults, not growing adolescents or pregnant or lactating women.

Fats are the most potent sources of energy we have. Another important function is that they serve as carriers for the fat soluble vitamins. Experimentally, it has been shown that certain unsaturated fatty acids are essential to the rat, but it is not known whether man needs these unsaturated fatty acids. At any rate it is most unlikely that our diets would ever be deficient in these substances. In our diet, fat is obtained from both animal and vegetable sources. Hydrogenated cottonseed oil is the basis of various substitutes for natural fats. Margarines are made from animal and vegetable fats. When vitamin A is added to margarine, it is as nutritious as butter in mixed diets for man.

Actual fat intake is influenced considerably by food habits. Generally fat furnishes from a fourth to a third of the daily caloric intake, which would mean that we consume around 100 grams of fat per day. But one can get along with less fat if sufficient carbohydrate is available for energy needs and if there are adequate sources of vitamin A available. This is usually possible because the body can synthesize vitamin A from the yellow pigment carotene which is present in most green and yellow vegetables. More fat is desirable in hard manual labor because of the increased caloric needs, which cannot be satisfactorily fulfilled by the more bulky carbohydrate foods.

Carbohydrate is plentiful in our diets. As with fat, the requirements for carbohydrate depend on activity, and actual intakes are graded largely on food habits. Because of its relatively low cost, and the ease with which it can be obtained, large amounts are consumed. A sedentary person may consume from 150 to 200 grams of carbohydrate per day, whereas an active person may consume three to four times that amount.

Certain inorganic or mineral elements are just as necessary to our health as are other nutrients. Experimentally with the rat it has been shown that some 12 minerals are necessary for good nutrition, but many of these are necessary only in minute amounts. Undoubtedly man also requires many of these minerals, but from the practical view we need consider only a few. Sodium and chlorine are needed in relatively

large amounts and are easily supplied by the use of ordinary salt. The inorganic elements in which our diets are most likely to be deficient are calcium and iron, and in the inland areas iodine should be considered.

Milk and cheese are the only rich sources of calcium in the diet, though small amounts are obtained from most vegetables and fruits. Meats are a poor source of calcium as also are eggs. The calcium requirement for adults is a much disputed question. There are some who believe that 0.1 to 0.2 gram per day is sufficient, and others who feel that 0.7 to 0.8 gram per day is desirable. Until better factual information is available, it might be well to adopt a middle of the road policy, or 0.5 gram which is approximately the amount of calcium furnished in a pint of milk.

Iron is furnished by meat, generously by liver. Other good sources are eggs, leafy green vegetables, potatoes, dried fruits, and whole grain cereals. The iron in foods is not completely available to the body but on the average, 60 to 70 per cent is available. An average intake of 10 to 12 mg. of iron per day will satisfactorily fulfill the normal adult's requirement for this nutrient.

Iodine is needed only in small amounts, probably of the order of 0.2 mg. per day, and is adequately furnished by the use of iodized salt.

There are four fat soluble vitamins, and of these only vitamins A and D are of practical importance in the normal nutrition of man. The best sources of vitamin A are liver, egg yolk, whole milk, cream, and butter or enriched margarine. We can also utilize a substance from dark green leafy vegetables and from yellow vegetables, the pigment carotene, which in the body is converted into vitamin A. Another factor in our favor is that we have the capacity of storing, particularly in the liver and kidney, rather goodly amounts of vitamin A. Thus in the summer when an abundance of fresh vegetables is available, we may store vitamin A to help us through the winter.

The recommended daily dietary allowance of vitamin A for adults is 5000 I.U. per day. This amount of vitamin A is readily obtained from an intelligent selection of food, particularly if a serving of a dark green leafy or yellow vegetable is included daily. Lettuce is not a dark green leafy vegetable, particularly iceberg lettuce.

Concerning vitamin D, little is known about the requirement of adult man, but it undoubtedly is small. Few foods contain an appreci-

able amount of vitamin D. For it we depend principally on sunshine, except in infants and children where fortified milk may be used and where it is strongly advisable to use a fish liver oil or other rich source of this vitamin.

There are some 15 water soluble vitamins that have been described in experimental nutrition. Of these only four are of importance, as far as is known today, in practical human nutrition. These are ascorbic acid and three members of the vitamin B-complex—thiamine, riboflavin, and niacin. It is important to know that we do not have the ability to store the water soluble vitamins for any length of time as is the case with the fat soluble vitamins. Thus we must provide them in our diet regularly.

Ascorbic acid is obtained principally from citrus fruits, from tomatoes, or from raw cabbage. It is also obtained from salad greens, other fruits such as strawberries, peaches, and melons, and from potatoes when cooked in the skin. It is well to remember that ascorbic acid is readily destroyed by contact with air, particularly at an elevated temperature. The recommended dietary allowance for ascorbic acid is about 50 to 75 mg. per day which is the amount furnished by the juice of one large orange or contained in two glasses of tomato juice.

The vitamins of the B-complex are obtained chiefly from the protein foods and from the whole grains. Thiamine is present in large quantities in pork and liver and in good amounts in legumes, egg yolk, nuts, and whole grains or enriched flours. There is much riboflavin in milk and liver, and fair amounts in legumes and whole grains. Niacin is present in generous amounts in liver and other meat and also in whole grains and enriched flour; it is low in milk. The recommended daily allowances for the average adult for these three vitamins as given by the Food and Nutrition Board of the National Research Council are 1.8 mg. for thiamine, 2.7 mg. for riboflavin, and 18 mg. for niacin. It is quite probable that the figure for riboflavin—that is, 2.7 mg. per day—is high, and that a value of 2.0 mg. per day is a more reasonable recommendation.

Summarizing the available information on nutritional requirements for the adult, one could say that calories are required in an amount sufficient to maintain or adjust weight to a desirable level. Fat and carbohydrate are used principally for this purpose. Protein is recommended at a level of 1 gram per kilogram of body weight per day.

Minerals are adequately supplied by the use of meat or fish and vegetables, a reasonable amount of milk and cheese, and the use of iodized table salt. Vitamin A is the only fat soluble vitamin with which we need be concerned in normal adults. It is provided well through the use of egg yolk, liver, butter, enriched margarine, whole milk, tomatoes, and green or yellow vegetables. Of the water soluble vitamins, ascorbic acid is adequately provided by the daily use of citrus fruit, tomatoes, or raw cabbage. Thiamine, riboflavin, and niacin are well supplied by the protein foods particularly if some milk and whole grain or enriched cereals are included. As far as is known today, other nutrients still largely in the investigative stage, so far as they are required by man, are probably furnished in satisfactory amounts by the intelligent selection of good wholesome food.

The use of specific vitamins or vitamin mixtures in medical treatment should be based, it seems to me, on the best available information on what is considered to be the body requirements. It is impossible to give specific details of treatment, for like all other therapy it should be planned for each specific case. Unless there are conditions which prevent the normal ingestion or assimilation of food, an early and important therapeutic procedure is to make sure the person consumes a really good diet, so that he actually receives good nutrition. If the history, or clinical or laboratory findings suggest specific vitamin deficiencies, supplemental therapy, either orally or parenterally, as the situation suggests, is desirable. The following are useful ranges of specific vitamin dosages:

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| <i>Vitamin A</i> | Preventive Treatment — 2,000 to 5,000 I.U. per day |
| | Therapeutic Treatment—10,000 to 30,000 I.U. per day |
| <i>Ascorbic Acid</i> | Preventive Treatment — 25 to 50 mg. per day |
| | Therapeutic Treatment—100 to 300 mg. per day |
| <i>Thiamine</i> | Preventive Treatment —1 to 3 mg. per day |
| | Therapeutic Treatment—3 to 10 mg. per day |
| <i>Riboflavin</i> | Preventive Treatment —1 to 3 mg. per day |
| | Therapeutic Treatment—3 to 10 mg. per day |
| <i>Niacin</i> | Preventive Treatment — 5 to 20 mg. per day |
| | Therapeutic Treatment—50 to 300 mg. per day; when using these amounts, niacinamide is preferable. |

We have found it convenient in preventive treatment in outpatient work and on the ward, to use an elixir of the water soluble vitamins made up so that 4 ml. or 1 teaspoonful contains 1 mg. of thiamine, 1 mg. of riboflavin, 10 mg. of niacin, and 25 mg. of ascorbic acid. This is inexpensive and convenient to prepare. At a dosage preferably of 4 ml. twice a day, it is entirely adequate for preventive treatment and can be well used in conjunction with therapeutic treatment.

Dried yeast is a convenient, effective, and inexpensive material to use in nutritional therapy. It furnishes not only vitamins of the B-complex, but also good quality protein, and when used in generous amounts it also contributes appreciably to the total protein, as dried yeast averages 40 to 45 per cent protein. But to administer effective amounts of yeast in preventive or therapeutic treatment, it is almost necessary to dispense it in bulk. Yeast tablets simply do not furnish enough yeast, even if one is willing to take ten to fifteen tablets a day. The average yeast tablet contains a little less than a half-gram of yeast so that even ten tablets per day would furnish not more than 5 grams of yeast. We have found it successful in preventive treatment to dispense 15 grams of dried yeast per day—with brewers' yeast this amounts to about one heaping tablespoonful—and to use two to three times this amount in therapeutic treatment. Only rarely do we find individuals who have gastrointestinal distress following ingestion of this quantity of dried yeast when it is divided into two or three doses per day. It is conveniently given in cold tomato juice. In fact a six or eight ounce glass of tomato juice with one or two heaping tablespoons of dried yeast is about the most effective and inexpensive type of generally good nutritional therapy. It furnishes significant amounts of vitamins A and C as well as vitamins of the B-complex and good quality protein. It is really nutritional therapy, not vitamin therapy.

It is well to consider therapy with the water soluble vitamins whenever parenteral fluids, particularly glucose, are given. Patients receiving parenteral fluids are usually not consuming adequate diets and since the water soluble vitamins are not stored in body tissues for any length of time, it is advisable to give them along with parenteral fluids. Recently there have appeared on the market convenient preparations of some of the B-complex vitamins in a form suitable for intramuscular injection, or for addition directly to the infusion material. I know of

none of these preparations which also contains ascorbic acid, but ascorbic acid should be included along with thiamine, riboflavin, and niacin in conjunction with parenteral fluids.

The use and abuse of vitamins simmers down to whether there is any need for them in the specific case in question. It is not an abuse to use them in investigative medicine or in any condition where there is any reasonable evidence or belief that they have been received in insufficient amount, and that their addition will be helpful. But it is not proper to publish premature and enthusiastic announcements regarding therapeutic findings. So frequently these are based on only a few cases with no adequate controls. This is most unfortunate because it arouses false enthusiasm and furnishes ideal material for exploiting the public. When these claims are tried and found wanting, one tends to be skeptical of other nutritional information which is really sound. As examples of unfortunate and extravagant claims one may mention the use of large amounts of vitamin A in the treatment of hypertension, of vitamin B₆ or pyridoxine in the treatment of Parkinson's syndrome, of thiamine in the relief of pain following dental extraction, of vitamin K in the prevention of dental caries, of calcium pantothenate or para aminobenzoic acid to restore gray hair to its natural color, and of pyridoxine in the treatment of acne vulgaris.

Probably the public is the greatest abuser of vitamin preparations, but the public is not solely at fault. It has been bombarded with misleading advertising and led to believe that a half to two thirds of our entire population is malnourished, and that if one is weak, tired, and fatigues readily, it is probably because he is one of the two thirds of the population that is not properly nourished. That may be the case, but it also may not be so. The result, unfortunately, is a tremendous misuse of valuable and expensive material. In most cases a more intelligent approach would be to improve one's selection of food—that is, if nutrition is at fault.

Many vitamin preparations now on the market contain small amounts of calcium pantothenate, of pyridoxine, and of mixed tocopherols—yet there is no evidence that man is ever deficient in these substances or is benefited by additional amounts. So why should they be added to vitamin preparations sold to the public? Their use in investigative medicine and experimental nutrition is one thing, but dispensing them to the public is another matter.

There is excellent evidence that inadequate nutrition does impair health, that it may cause specific diseases, and that it may predispose and aggravate other diseases. There is also good evidence, not only with experimental animals but with man, that really "excellent nutrition" over generations does result in marked improvement in general health, in greater resistance to disease, and in better physical fitness. But vitamins are only part of nutrition, and there is no evidence that man will become less fatigued, experience any fewer colds, or have more general resistance to disease by consuming "extra" amounts of various vitamins. May I repeat, good nutrition comes from a wide choice and a wide variety of wholesome food, not from a poor diet supplemented with vitamin and mineral preparations.

Let us examine briefly the recent claims that a large portion of our population is malnourished. These have generally resulted from various dietary surveys conducted on sizable groups of people in various parts of the country. In these studies it has generally been found that a large percentage of the subjects were consuming one, or generally several, nutrients in amounts less than those advised by certain dietary recommendations—generally recommendations based on very inadequate evidence, recommendations set at a level thought to be desirable for optimum health and well-being, and recommendations almost identical with those made in this paper. The implication has developed from these survey studies that a third, or a half, or two-thirds of the population are malnourished, and consequently not in the best of health. But seldom in any of these studies was evidence obtained concerning the status of health. True, a large majority of the people were malnourished, in comparison with certain recommended dietary allowances, but I do not believe there is evidence that any individual or group of individuals has impairment of health to any measurable degree, if they receive 50 mg. of ascorbic acid rather than 75; if they receive 1.5 mg. of riboflavin rather than 2.7, and so forth. But on the other hand no one has proved, as far as I know, that at these lower levels one enjoys as good health as at the higher levels. Do not misunderstand me—I do not feel that the recommended dietary allowances of the Food and Nutrition Board are not a good thing. They definitely are. There was a positive need for a set of dietary allowances supported by an authoritative group of individuals. They are a goal for optimum nutrition. They are subject to revision on sound experimental evidence, and they are an excellent guide

for preventive and therapeutic nutritional therapy. They are what they are entitled—"recommended dietary allowances." But it is certainly not sound to imply any degree of ill health solely on the basis of not meeting one or more of these recommendations.

There have been attempts in recent years to appraise the nutritional status of individuals by laboratory methods and special instrument methods. By the latter I refer specifically to the use of the slit lamp or biomicroscope for observing ocular changes in riboflavin and vitamin A deficiency, tongue changes in niacin deficiency, and gum changes in ascorbic acid deficiency. Literally hundreds of investigators have made studies of the plasma ascorbic acid, but there is no evidence that an individual with 0.4 mg. per cent ascorbic acid is any different from the viewpoint of health than one with 0.6 mg., a figure generally given as a desirable plasma level; it is thus not sound to say or imply that individuals with 0.4 mg. ascorbic acid are malnourished. The plasma ascorbic acid appears to be a measure of nutritional adequacy but not of inadequate nutrition. More recently ascorbic acid estimations have been done on white blood cells and here it appears that one gets a measurement of inadequate nutrition.

The vitamin A and carotene concentration in the blood can be estimated with reasonable accuracy and ease; but their interpretation in terms of health is most unsatisfactory, and there is no sound evidence to say that a person with 70 I.U. of vitamin A differs in health or well-being from a person with twice that concentration of vitamin A in the blood.

Corneal vascularization as a morphologic manifestation of riboflavin deficiency was first observed in the rat. Shortly thereafter it was observed in five or six other conditions and hence by itself cannot be accepted as a specific sign of riboflavin deficiency. The use of the biomicroscope in observing ocular changes in vitamin A deficiency, and tongue and gum changes in early niacin and ascorbic acid deficiency, is definitely in the investigative stage. It is one thing to observe and describe morphologic changes, and it is entirely another matter to show that these changes are the result of inadequate nutrition. Even response to specific therapy is not acceptable proof when it is necessary to continue the therapy for periods of a month or more. This particularly applies to observations on tissues such as the conjunctiva, tongue, and gums which are so readily subjected to minor infections and trauma.

There have been a number of classic investigations giving evidence

of the importance of improved nutrition on health, and I should like to mention briefly a few of these. Thus Robert McCarrison² in studies on two tribes in India found unmistakable evidence of the value of superior nutrition. In one of his papers he says: "For some nine years of my professional life, my duties lay in a remote part of the Himalayas where there are located several isolated races far removed from the refinements of civilization. Certain of these races are of magnificent physique, preserving until late in life the characteristics of youth; they are unusually fertile and long lived, and endowed with nervous systems of notable stability. . . . These people live on a very frugal diet, apricots, vegetables, goat's milk and butter—whole grains and meat only on feast days."

Then McCarrison studied a tribe in the south of India where the diet for generations had consisted of polished grains, vegetable fats, little milk, no meat, and few vegetables. The stature of this tribe was stunted, illness was common, mortality high. Now obviously there were genetic differences between these people, and environmental factors other than nutrition. But following his observations of these two tribes, McCarrison took a thousand albino rats and fed them for two and a half years on a mixed diet representative of one tribe. Another thousand rats were fed the diet of the other tribe. The differences found were even more striking with the rats than they had been between the tribes. It is of interest that this classic experiment was repeated on rats only a year ago by another investigator, and essentially the same results were obtained.

Orr and Gilks³ conducted a study of two South African tribes with a view to possible improvement of physical efficiency through improved diet. These tribes live in regions which do not differ as to climate and agricultural possibilities. The adult males of one tribe average 5 inches taller and 23 pounds heavier than corresponding subjects in the other tribe. Muscular strength was found by dynamometer tests to be 50 per cent greater in one tribe. There were marked differences in the height and weight of the women of the two tribes. But the most striking differences occurred among the children. Of the children up to 8 years of age, both girls and boys, three-fourths in one tribe were graded as in good physical condition; in the other tribe only one-fourth were graded in good physical condition. Skeletal deformities, dental caries, spongy gums, anemia, diseases of the skin, and tuberculosis were rare in one tribe, most common in the other.

There were undoubtedly genetic differences between these peoples

but there were also significant dietary differences. One tribe consumed large quantities of milk, meat, and blood. The other tribe, while they raised large herds of goats, treasured them as wealth—not as food. They lived mostly on cereals and roots.

The classic study of Dr. Correy Mann⁴ on English schoolboys should certainly be mentioned in any discussion dealing with nutrition and improved well-being. The experiments were carried out over a four year period on approximately 200 boys of 6 to 10 years of age. They show clearly the value of extra milk in improving health on diets which were thought to fulfill all nutritional needs. Those on the best diet—the basal diet plus a pint of milk per day—gained approximately 7 pounds per year as compared with 4 pounds per year on the control diet. In height there was also an increased gain. Throughout the four year period there was striking improvement in general fitness, fewer upper respiratory infections and other illnesses, and improved mental capacity. Dr. Mann states that these factors are difficult to measure and evaluate, but emphasizes that an impartial observer had no difficulty in pointing out quickly which boys were receiving the improved diet.

For many years Sherman⁵ and his students at Columbia have been doing long term studies with rats, which advance the principle of *the nutritional improvability of what some consider the normal*. These animal feeding experiments have been carried on for many generations and with a rigorous regard for exactness. The basal diet used by Sherman in these studies consisted of 1/6 dried whole milk and 5/6 ground whole wheat plus salt and distilled water. Such a diet reared rats successfully through several generations. But improvement in the diet by having only a larger proportion of milk, improved greatly what could be considered the normal for the rats receiving less milk. Rate of growth and efficiency of growth were increased, as were average size, time required to reach maturity, time of full adult capacity, vitality as indicated by success in the launching of successive generations, and actual length of life.

Two years ago Ebbs, Tisdall, and Scott⁶ published their now well known paper on the influence of prenatal diet on the mother and child. "The prenatal diets of 400 women with low incomes were studied. One group found to be on a poor diet was left as a control, a second group on a poor diet was improved by supplying food during the last three or four months of pregnancy, and a third group, found to have

moderately good prenatal diets, was improved by education alone. During the whole course of pregnancy the mothers on a good or supplemented diet enjoyed better health, had fewer complications, and proved to be better obstetrical risks than those left on poor prenatal diets. The incidence of miscarriages, stillbirths, and premature births in the women on poor diets was much increased. The incidence of illness in the babies up to the age of six months and the number of deaths resulting from these illnesses were many times greater in the Poor Diet Group."

In the *Journal of Obstetrics and Gynecology* for July 1943⁷ is a report of some of the nutritional studies that the Harvard School of Public Health has conducted on the growth and development of the well child. These investigations are unusually significant in that they go back over a period of 12 years. All of the children in the study, of which there were originally 324, have actually been studied from birth, and before birth by antepartum studies on the mother. The complete studies include not only detailed and carefully conducted nutrition histories, but obstetric, pediatric, roentgenologic, dental, anthropometric, psychologic, and some laboratory studies.

This recently published work on 216 women and their infants, using the oldest sibling in each family, has shown a statistically significant relationship between antepartum diet and the condition of the infant at birth. In the 216 cases studied, every stillborn infant, every infant who died within a few days of birth, with the exception of one, the majority of infants with marked congenital defects, all premature and all "functionally immature" infants, were born to mothers whose diets during pregnancy were inadequate. From this study it would appear that if the mother's diet during pregnancy is excellent, her infant will in all probability be in excellent physical condition.

As in the study of Ebbs, Tisdall, and Scott, a significant relationship was also found to exist between the prenatal diet and the course of pregnancy. The findings with regard to eclampsia were most striking. In these 216 women there were 29 cases of eclampsia of varying degree. There was no incidence of eclampsia in those women with good or excellent diets; most of the cases of eclampsia were in those on poor diets, a few in the fair diet group.

Thus in the few studies briefly mentioned, all but one of which were done on human subjects, there seems to be good evidence that improved nutrition over long periods results in better health. There is also good

evidence that good nutrition is of profound importance during pregnancy, both for the mother and for the health of her infant.

But let us recognize that there is not convincing objective evidence that "excellent nutrition" is really a factor of major importance in the ordinary diseases we see, and that the best of present day biochemical techniques and special instrument methods do not give specificity in diagnosis. Most of those who have responsibilities for the health of individuals question the actual importance of "excellent nutrition" as compared with what one might call "average nutrition" in the majority of patients seen. There are several reasons for this. Nutrition is a relatively new science. Medicine is much, much older. It takes time for new principles to be adopted—unless, and this is important, there is a finding of dramatic importance to a specific disease. Medical training and thought, and environment in the clinical sciences, are in terms of disease, diagnosis, pathology, bacteriology, and wishful hopes, or justly proud admiration of dramatic cures—not in terms of health, preventive medicine, of longtime results. Nutrition, even today, is inadequately taught in most medical and public health schools.

As positive measures of how nutrition may be of more help to medicine and hence to society, may I suggest the following:

1. Nutrition should be introduced into the medical and public health schools to an extent and in a manner comparable to its importance.

2. It would be well if more of our medical schools had in each of the four main departments—medicine, surgery, obstetrics, and pediatrics—an individual trained not only in this field but also in nutrition.

3. A really high grade nutrition clinic should be established in a few representative regions of the country, not as a separate clinic, but as a part of a good general medical clinic, a good obstetrical clinic, and a good pediatric clinic, so that the outpatient records of these clinics would have detailed nutritional histories, laboratory findings, and clinical findings, on repeated visits, and over extended periods. Frequently on the ward we have patients who have been seen repeatedly over a period of several years in the outpatient clinics, and careful nutrition records of the previous years would help in establishing any relation between nutrition and their present condition.

4. Attempts to study growth and development in the well baby from before birth, that is antepartum studies on the mother, and through infancy, childhood, adolescence, and adulthood should be encouraged.

These studies should combine the best in clinical observations, the best in laboratory procedures, and the best in nutritional techniques. And we must not expect to get the full answers too quickly—it will take time.

Nutrition means more than vitamins—it is the science of food and its relation to health, and as such it is inseparable from any concept of medicine. But for nutrition to be of greater value to medicine we must seek objective and sound information relating it to the etiology and therapy of the common diseases we see.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



MAY 1944

CANCER OF THE COLON

HENRY CAVE

Attending Surgeon, The Roosevelt Hospital

CANCER of the colon is amenable to surgical extirpation. Only in so far as diagnosis is concerned is it a medical disease. It has been and can be diagnosed by the physician, but it should not be treated by him. All physicians should be keenly aware of the early signs and symptoms if any exist. All new chemotherapeutic measures have failed to retard in any measure or influence its development. Irradiation with x-rays or radium on a primary colonic growth is valueless. If attacked surgically before metastasis has taken place, a longer period of cure can be expected than in cancer of any other part of the gastrointestinal tract. It is considered usually, a disease of advancing years; but not infrequently it is discovered in the third and even the second decades of life. When found in the younger age groups it is usually of a violently malignant nature and the morbidity and the mortality are high. Deaths from cancer of the colon are second to cancer of the stomach in malignancies of the gastrointestinal tract.

In the City of New York with a population of 7,300,000 persons in the year of 1942, the Bureau of Vital Records and Statistics shows that

* Read before the 16th Graduate Fortnight of The New York Academy of Medicine, October 21, 1943.

1,962 individuals died of cancer of the stomach. In that same year 1,616 people died of cancer of the colon and also in this same year there were 911 people who died of cancer of the rectum.

I have been unable to find any statistical data which would suggest that cancer of the large intestine is on the increase. Yet due to the ever increasingly laudable attitude of the laity, towards the value of the x-ray as a precise aid in diagnosis, many more colonic tumors are discovered suggesting perhaps an increased incidence.

This Graduate Fortnight fostered by The New York Academy of Medicine is attended largely by physicians with a scattering of surgeons, therefore, this presentation will deal mainly with the physiology, the symptomatology and the methods of early diagnosis and not operative procedures except in generalities.

ANATOMY AND PHYSIOLOGY

In order to appreciate adequately the symptom-producing mechanism of colonic growths it seems timely to re-emphasize briefly certain anatomic and physiologic facts.

This discussion does not include the rectum. The colon begins in the right iliac fossa and ends opposite the body of the third sacral vertebra, where it fuses with the rectum. The size of the colon and the thickness of its musculature has considerable bearing on the rapidity with which symptoms appear. The cecum is large, thin-walled and its diameter is approximately 6 cm. as contrasted with the diameter of the sigmoid which is 2.5 cm. The thickness of the wall increases from the cecum down to the descending colon and the sigmoid. Fecal matter which is poured into the cecum through the ileo-cecal valve is quite liquid and as it nears the sigmoid segment it becomes thicker. Due to the anatomic arrangement of the ileo-cecal valve, malignant involvement of the cecum in this region causes obstruction early. Tumors particularly the fungoid type growing in the cecal wall have plenty of room for development and expansion, hence obstruction comes late, if ever. Fungoid, ulcerating and cicatrizing growths of the left colon and sigmoid all necessarily produce obstruction earlier due to the smaller caliber of this segment of the large bowel.

SYMPTOMS

In discussing symptoms, it might be well to divide the colon into

two halves: (1) the cecum, the ascending and right half of the transverse colon; (2) the left half of the transverse, the descending and the sigmoid colon. It is a noteworthy fact that cancer of the colon, in its earlier stages usually produces symptoms which are decidedly vague, frequently bizarre and often insidious. I question whether or not authors writing on the early diagnosis of cancer of the colon are right in assuming that malignancy of the colon is ever diagnosed early. It is the complications of cancer and not the growths themselves which give symptoms.

There are various other lesions of the colon and diseases of the viscera outside the colon which produce symptoms similar to those of neoplasms of the large bowel, namely — diverticulitis, tuberculosis, ulcerative colitis, also chronic disease of the appendix, chronic cholecystitis, peptic ulcer and intermittent mild attacks of subacute pancreatitis.

When the lesion is once present, and all too frequently in a palpable form, cancer of the right colon presents symptoms of so-called "dyspepsia," marked anemia with loss of weight and strength. The earliest period of manifestation of cancer of the cecum and of the ascending colon may be a vague sense of bloating. Sometimes a mucous diarrhea will occur and the patient is aware of an alteration, even though slight, of the bowel habits. The old text-book story of alternating constipation and diarrhea frequently means that the growth has become of considerable size, far advanced, and certainly could not be classed as an early symptom, but as a later manifestation of the disease. The anemia, usually severe is by far the most characteristic feature of right sided growths. Any patient suffering from marked anemia, even though there have been no symptoms or signs of malignancy of the colon, should be investigated for this disease. Why is it that the anemia is more marked with cancer of the cecum and ascending colon than it is with cancer of the left half of the colon? We all know that it is seldom that sudden sharp hemorrhage springs from a right sided growth; hence, this severe anemia must be due to the fact that the growths are usually large in the right colon, the oozing surface extensive and that there is an increased absorptive area for toxic substances. Tenderness and the presence of a palpable mass in the cecum or the ascending colon is generally a late sign, yet there have been a few instances where we have elicited a history of pain and local tenderness in the early growths of this segment of the large bowel.

In cancer of the left half of the colon, the efforts to force the more solid fecal material down into the rectum past the partially or completely obstructing lesion which narrows the lumen of the descending colon produces pain. Increasing constipation is an almost constant complaint. The patients complain of bloating, abdominal distention and a feeling of general discomfort. I have observed a few instances of a vague intermittent slight distention as the only symptom of an early malignancy of the lower sigmoidal segment, and so often the discomfort is relieved by the passage of flatus.

Obstruction, either acute or of a chronic nature, may be the earliest symptom denoting the presence of a tumor of the left colon. We have been impressed by six instances of obstructive lesions of the left colon where the only symptom was pain and a feeling of localized distention in the right lower quadrant. All of these patients were operated upon primarily for appendicitis, and later came to secondary operations for the growth in the left half of the bowel. The reason for this pain in the lower quadrant, is due to the thinness of the cecal wall, the back pressure from the partial obstruction distends the proximal bowel especially the cecal head; the distention being the pain-producing mechanism.

Annular carcinoma of the sigmoid segment is capable of producing pain in the right upper quadrant. In one patient the pain was so severe she was operated upon for gall bladder disease. The gall bladder was found to be normal and a tight band across the pyloric end of the stomach was divided. Relief from vomiting was assured this patient; but, after three weeks time when the patient had returned home, right upper quadrant pain and persistent vomiting necessitated further study. Repeated and carefully taken roentgenograms failed to reveal the presence of a small tumor in the sigmoid which was found when this patient was subjected to an exploratory operation without a preoperative diagnosis having been made.

In order to obtain information which might prove helpful in the early diagnosis of neoplasm of the colon, Scudder Winslow of our Interne Staff has carefully reviewed and analyzed eighty-four of our case histories from the First Surgical Division of The Roosevelt Hospital. The cases were treated during the past decade (October 1, 1933 to October 1, 1943). The majority of these patients were individuals whom we see in the wards of our metropolitan hospitals, many in the

older age group, in poor physical condition, some undernourished and old for their years. Our findings were disappointing; for many were in the advanced stages of the disease when admitted.

Fifty per cent were either acutely or chronically obstructed upon admission. Forty-three or one-half of the total number complained of change in bowel habits, forty-three complained of abdominal discomfort of greater or lesser degree, nine localized their pain in the right lower quadrant. The average age of this group of patients studied was sixty years. There were an equal number of males and females. Loss of weight was frequently noted, usually ranging between ten to thirty pounds. The disease for the most part was self evident in the larger proportion of cases, not only from their general appearance, their cachexia but the presence of a tumor mass and signs of obstruction and positive findings by x-ray. Seventy per cent had well marked evidence of neoplastic disease as evidenced either by obstruction or by the presence of a palpable mass. Certainly there were but few instances where it could be stated that these patients sought medical advice in the early stages of the disease; and a most surprising fact was that relatively so few (22) gave a history of the passage of blood. In spite of the advanced neoplastic condition of these patients our operability rate was 78 per cent.

DIAGNOSIS

Judicious or injudicious, it is so rare that one can depend entirely upon vague abdominal symptoms to denote the presence of an early neoplasm of the colon that it seems justified, upon the slightest provocation, to employ immediately two fact-finding instruments of precision—sigmoidoscopy and radiography. Two factors are to be considered in demanding these two valuable aids in diagnosis: The first is to ease the anxiety of the patient who comes suspicious of malignancy; the second to give the physician exact information as to the presence or absence of an organic lesion. More than the mere routine barium enema should be insisted upon. The roentgenologist should *search* for the cause by means of mucosal studies of any suspicious abnormality in any segment of the colon. Numerous and repeated spot films should be taken at various angles. I re-emphasize the word "search," for by such admonition easily overlooked growths can be discovered. The many tumors of the lower sigmoid can be seen not only by the sig-

moidoscope but can be palpated by the finger in a properly conducted rectal examination.

SURGICAL TREATMENT

At the present time the treatment of nearly every disease is based upon factual findings. For instance, syphilis is treated after positive serologic tests have been made; malaria is treated after finding the plasmodium in the blood smear; pneumonia is treated only after the type has been specified; and cancer of the breast usually after biopsy and frozen section have been made.

The fundamental principles involved in the treatment of malignancy of the colon are: (1) Radical removal of the tumor and adjacent gland-bearing area; (2) Restoration of continuity of the bowel.

However, it may well be added that of almost equal consideration is the technical ability of the surgeon, the patient's condition, the pre-operative preparation of the patient.

Sixty-one of the cases herein reported were resected. Some of these were resected in the face of local extension or metastasis in the liver. There were eighteen deaths in the resected cases; there was a 29 per cent mortality. These deaths occurred in the hospital.

It is an amazing surgical commentary that although the Mikulicz operation has had heaped upon it severe criticism, yet many of the ablest surgeons have abandoned other procedures and seem convinced that the method of Mikulicz, on account of its being so eminently safe, and if properly done, adequate in the radical removal of the tumor and its gland-bearing area, is unquestionably the procedure of choice.

In the past sporadically and especially at the present time there appear enthusiastic proponents of primary resection with or without complementary decompression. This, no doubt, has resulted from an endeavor, ideal in its conception, to remove all malignant tissue and to restore bowel continuity by various aseptic techniques, over various newly invented instruments, in the shortest possible time.

Specifically, it may well be stated that for tumors of the right colon there are three suitable procedures which may be utilized, depending upon the particular lesion and complications encountered: (1) Primary resection of the colon with end-to-end, or side-to-side anastomosis. (2) A one or two-stage manoeuvre: First stage, ileo-transverse colostomy, either side-to-side or end-to-side. Second stage, extirpation of

the right colon with its tumor-bearing area. (3) Primary resection of the right colon with utilization of the Mikulicz principle of a gun barreled ileum to transverse colon as suggested and carried out so successfully by Lahey.

For tumors of the right colon I prefer a one stage procedure in the non-obstructed group, especially where we have been able to place preoperatively the distal end of the Miller-Abbott tube at or near the ileocecal valve.

The Miller-Abbott tube has proven of unquestionable benefit in decompressing the terminal segments of the small bowel in obstructive lesions of the right colon; and whether a one stage procedure or a two stage manoeuvre is carried out the use of this tube has diminished the morbidity and mortality.

The presence of this tube put down forty-eight hours prior to operation will render any operation on any segment of the colon easier, for the reason that almost the entire small bowel is telescoped over this tube into a small mass and when operating on the right colon this small mass of intestines can be placed in the left side and when operating on the left colon, especially in resections of growths of the splenic flexure, it can be placed far over in the right side of the abdominal cavity.

Tumors of the transverse colon are easily managed by an exteriorization manoeuvre, obstructive resection or resection with primary suture side-to-side or end-to-end, preferably utilizing the advantage of a complementary cecostomy.

Left sided neoplasms, particularly of the sigmoid, can be removed by a properly performed Mikulicz procedure or resection with primary anastomosis open or closed according to the site and according to the preoperative preparation of the patient. An invaluable aid in mobilization of any left sided growth is dividing the spleno-colic ligament, mobilizing and drawing down the upper splenic and descending segments.

Rankin's obstructive operation with immediate removal of the tumor mass and complementary cecostomy is undoubtedly a valuable method. The dysfunctionalization of the left bowel as advocated by Devine has been received by some in this country with enthusiasm.

Although there has been a trend to resection of neoplasms of the left side with complementary decompression and primary end-to-end

suture, I am still of the belief that with the majority of surgeons the mortality may be kept lower and an equal number of cures effected if a properly performed and adequate exteriorization or an obstructive operation is carried out with complete removal of the gland-bearing area.

I hold no brief for any one type of resection in all cases. The Mikulicz operation, in the hands of most surgeons, where the gland-bearing area is removed, is certainly safer and is equally as adequate as any type of an intestinal anastomosis. Primary resection, with side to side anastomosis, is safer, in my opinion, than any type of end to end anastomosis over clamps, or by the so-called open anastomosis. However, there are certain instances where a primary resection and immediate anastomosis is justified, especially if there is no obstruction, or if preliminary cecostomy has been carried out.

I believe that the preoperative use of certain sulfonamides such as sulfasuxadine and sulfathaldine, have helped sterilize the fecal stream. I have, however, been unable to verify the complete value of this therapy in intestinal anastomosis, for I have always used about the anastomosis, sulfanilamide crystals. Sulfa drugs as adjuvants in intestinal surgery do not take the place of meticulous and thoughtful technique, and regard for adequate blood supply.

CONCLUSION

From the study of this somewhat limited group of malignancies of the colon, a good many points worthy of emphasis may be noted.

1. Our effort to obtain valuable information as to early signs and symptoms was fruitless.

2. More frequent use of the sigmoidoscope and the employment of the x-ray after barium enemas is to be emphasized in patients who come with the slightest suspicion of a disturbed gastrointestinal tract.

3. Needless to say any patient undergoing an abdominal operation of any magnitude whatsoever, should be hydrated; the fluid balance maintained; electrolytes at a high level; and plasma protein within the limits of safety.

4. If the growth is in the transverse, descending, or sigmoid colon, cecostomy should be performed, and for the most part, a good piece of the cecal head should be brought out on to the abdominal wall. There is too much danger in the use of a Pezzer catheter type of cecos-

tomy.

5. If the ileocecal valve is patent, and the tumor is in the cecum and ascending colon, the intelligent use of the Miller-Abbott tube to decompress the small bowel is a great advantage. The Miller-Abbott tube will render any operation on any segment of the bowel easier if put down forty-eight hours preoperatively. For the entire small intestine can be telescoped upon it.

THE PATHOLOGIC PHYSIOLOGY OF GASTRIC AND DUODENAL ULCER *

HARRY SHAY

GASTRIC and duodenal ulcers situated as they are in different organs, nevertheless produce profound changes in function in the stomach. It is not singular that gastric ulcer causes such changes. It is not evident, however, why duodenal ulcer, a lesion beyond the stomach, should alter gastric function so often and so strikingly. It is my assignment to demonstrate the changes in gastric function produced by these lesions and to present an explanation for them compatible with the character and location of their pathology. I shall limit my discussion to uncomplicated gastric and duodenal ulcers.

Gastric and duodenal ulcers cause alterations in gastric motor and secretory functions. The changes in motor function, the roentgenologist utilizes in his diagnosis of these lesions; the alterations in secretion revealed by fractional gastric analysis, though not diagnostic, frequently yield information exceedingly helpful in clarifying the clinical picture, and in suggesting therapy. It is periodically said that the data derived from fractional gastric analyses do not justify the time consumed by the procedure. With this point of view I do not agree. It is not intended that the results of fractional gastric analysis alone be diagnostic of any disease. But, evaluated along with the rest of the clinical picture, information obtained from fractional gastric analysis more than justifies its use.

The primary x-ray signs of niche, accessory pockets, and organic hour-glass constrictions are of little interest to us for this evening's discussion, since they represent anatomic changes. Any alterations in motor function which they produce are to a great extent due to altered mechanics rather than to changed functional mechanisms. In the secondary, or indirect, signs, especially in duodenal ulcer, we see striking changes in gastric motor function that have long demanded explana-

* Lecture delivered October 13, 1943 at the Sixteenth Graduate Fortnight of The New York Academy of Medicine. From the Medical Research Laboratory, Samuel S. Fels Fund, Philadelphia.

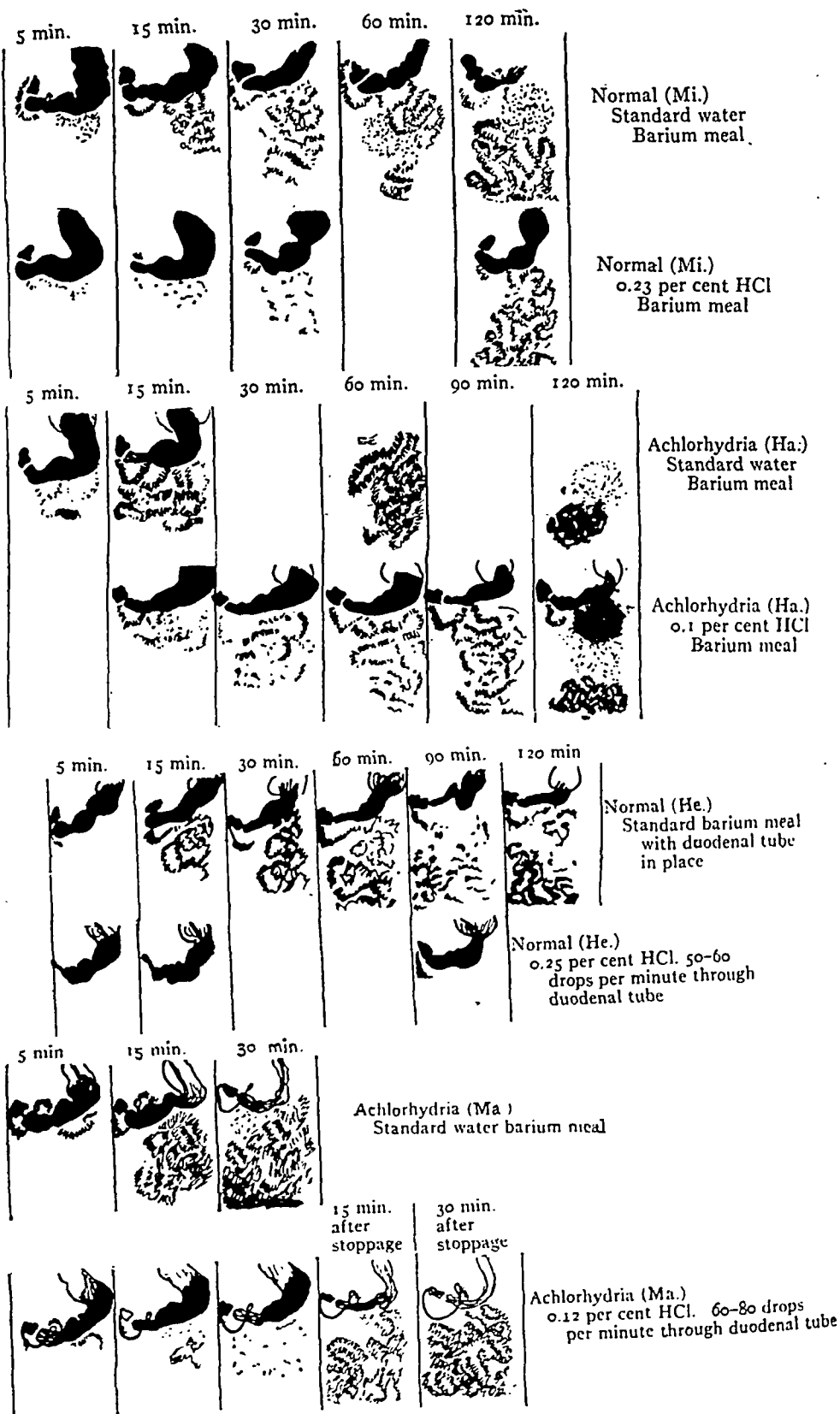
tion. These indirect signs consist of changes in gastric motility and evacuation. The former result in hyperperistalsis and hypertonicity and the latter in rapid gastric emptying.

The spastic manifestations of incisura, spasmodic hour-glass and diffuse gastropasm, seen in gastric ulcer, may be explained as initiated by the direct irritant action of the lesion upon the local musculature or upon related nervous structures (Auerbach's, Meissner's plexuses). A change in gastric emptying, if present in gastric ulcer, takes the form of motor delay. Except in lesions near the pylorus, this may be the result of (a) *reflex pylorospasm* and (b) *impaired gastric peristalsis and tonus*.

The altered gastric motor function in uncomplicated duodenal ulcer expressed by hypertonicity, hyperperistalsis, and rapid gastric emptying, does not permit of so ready an explanation. From results obtained through studies in the human subject during the past fifteen years, we believe we have come to an understanding of the mechanism which produces these altered gastric motor functions. To explain the changes, however, we should first consider certain phases of normal gastric motor activity.

The normal evacuation of gastric contents is dependent upon gastric tonus, gastric peristalsis, and the activity of the pyloric sphincter. From roentgen studies in the human subject, we¹ have concluded that the activity of the pyloric sphincter is of primary importance in gastric emptying. Thomas,² from studies in the dog, believes that antral activity is the chief factor in normal evacuation, an opinion shared by Quigley.³ This difference of interpretation is not germane to our present discussion. However, the now generally accepted opinion that the duodenum houses a mechanism which exercises an influence over all three (gastric tone, peristalsis and pyloric sphincter) is vital to the development of an adequate explanation for the disordered gastric function seen in uncomplicated duodenal ulcer.

Almost invariably, modern textbooks on human physiology state that the theory propounded by Cannon, that the pylorus is controlled by acidities of the gastric and duodenal contents, has been disproven. With such statements we are not in complete agreement. The first half of the Cannon theory—that a high acidity on the gastric side of the sphincter causes the pylorus to open—has been disproven. However, the second part of the theory that an adequate acidity on the duodenal



side has an ability to delay gastric emptying we¹ have been able to prove repeatedly in the human subject. This action is demonstrated if gastric evacuation of a standard meal is studied in normal individuals, and especially in achlorhydric subjects. If a person with a normal gastrointestinal tract and a normal gastric secretion is given 250 cc. of a water-barium sulphate mixture after an adequate fast period, his stomach will empty in from 60 to 120 minutes. When we repeat this study using a weak hydrochloric acid solution instead of the water, gastric emptying will be delayed. The delay in gastric emptying produced by an acid meal will be especially marked if the test subject has gastric achlorhydria. When a similar weak hydrochloric acid solution is dripped slowly into the duodenum and the test meal is administered orally, the marked delay in gastric emptying shows that the cause for these changes does not lie in an action of the acid on the gastric side of the pyloric sphincter (Fig. 1). The gastric hydrochloric acid really acts as the intrinsic agent which stimulates a duodenal mechanism concerned with the inhibition of gastric emptying. The inhibition persists until the pH of the proximal duodenum is raised to that level at which activation of the mechanism ceases. There is then further gastric empty-

Figure 1

Artists pen and ink drawings made to scale from X-ray films.

Row 1—Gastric emptying of 250 cc. water plus 2 oz. barium sulphate mixture in an individual with a normal gastric acidity response to an Ewald type meal.

Row 2—Gastric emptying in the same person when 0.23 per cent hydrochloric acid was substituted for the water. Note the considerable delay in gastric emptying produced.

Row 3—The gastric emptying of the water and barium meal in a patient with gastric achlorhydria.

Row 4—Note striking change in gastric evacuation when only 0.1 per cent hydrochloric acid was substituted for the water.

Row 5—Gastric emptying of water and barium meal in a person with a normal acid response to the Ewald type meal and a duodenal tube in place. No instillation into duodenum had been made.

Row 6—Gastric emptying of the water and barium meal in the same individual, when hydrochloric acid (0.25 percent) was instilled into the duodenum at the rate of 50-60 drops per minute. Instillation was begun with the administration of the water and barium meal by mouth. Gastric evacuation was completely inhibited. At 90 minutes when considerable gastric emptying had taken place when no duodenal instillation had been done, now showed no barium beyond the 2nd portion of the duodenum where the tip of the duodenal tube was located, through which the acid was instilled.

Row 7 and 8—Results of similar experiments performed in an achlorhydric subject. *Row 8* illustrates the rapid adjustment in the duodenum when the acid instillation is stopped. With practically complete inhibition of gastric emptying, while the acid was instilled into the duodenum, gastric emptying progresses rapidly in the first 15 minutes after the instillation is stopped and is complete in 30 minutes.

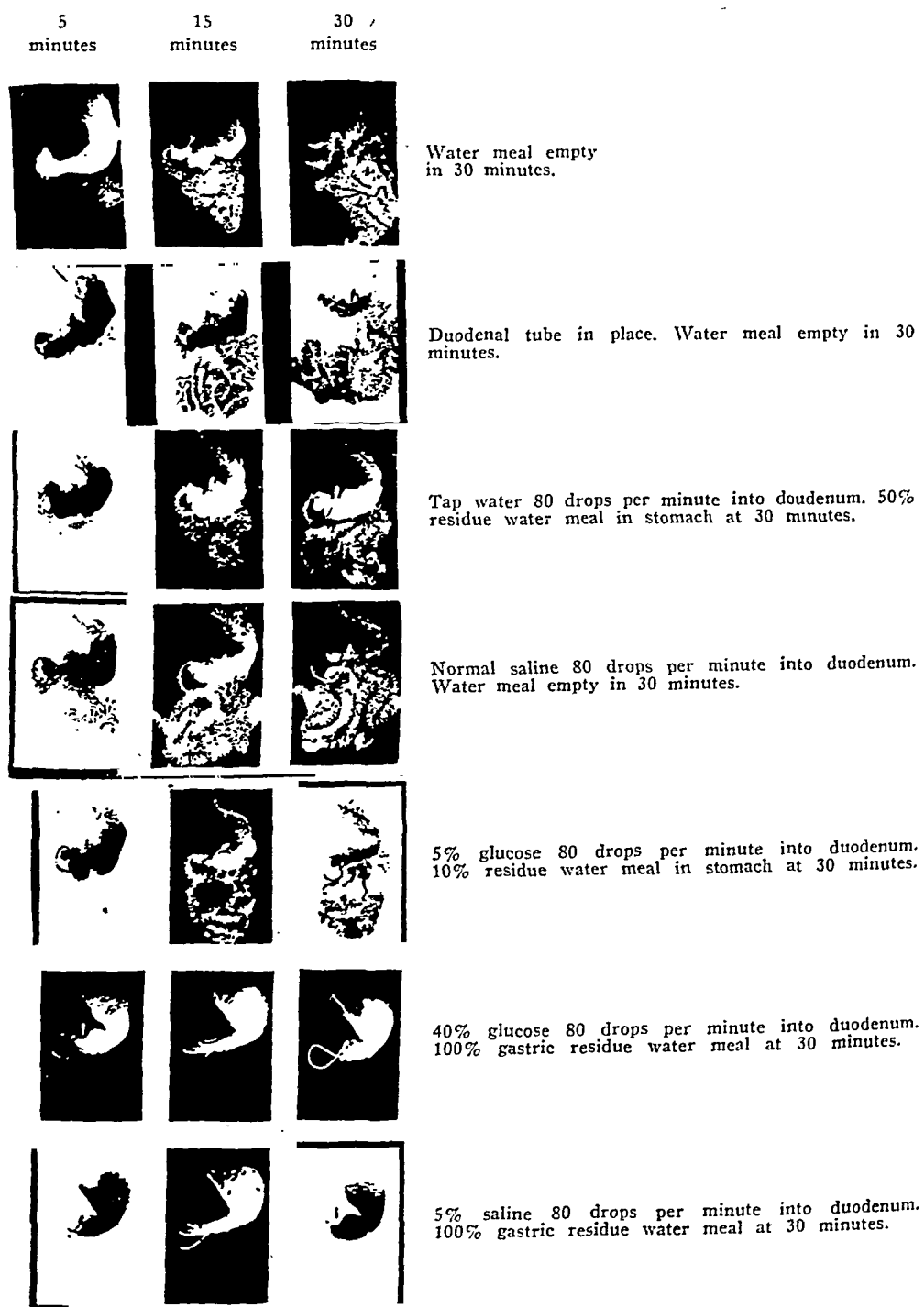


Fig. 2—Legend, see following page.

ing and the above process is repeated, resulting in the rhythmicity of gastric evacuation encountered in the normal individual.

While gastric emptying may thus be greatly influenced by the entrance of hydrochloric acid into the duodenum, we have shown and repeatedly stressed the fact that such an effect can be caused by agents other than the acid.⁴ The mechanism in the duodenum may be activated by foods as well as by other substances capable of altering the physical or physico-chemical conditions in the duodenum. Delay in gastric evacuation has been produced with hypertonic solutions of electrolytes such as NaCl, NaHCO₃, and non-electrolytes like glucose and also by fats and fatty acids. The action of fat is particularly basic to an understanding of the prominent part played by milk and cream in the ulcer diet. Foods, however, in order to be able to activate the duodenal mechanism, must reach the duodenum in proper concentrations or in proper form. In the stimulation of the duodenal mechanism the action of the hydrochloric acid depends on the duodenal pH produced, since in hypotonic solutions it is very effective. For the action of the salts and glucose, hypertonicity of the solution is a prerequisite. This obviously does not apply to fats, since they are insoluble in water. The local physiological actions of the various substances in the duodenum may be quite different, yet the gastric motor end result is the same in each, namely, delayed gastric emptying (Figs. 2 and 3).

Figure 2

Illustrating the effect of osmotic conditions in the duodenum upon gastric evacuation. An achlorhydric subject was selected for this illustration in order to eliminate the action of the intrinsic gastric acid stimulus of the normal individual.

Row 1—Gastric emptying of standard water and barium meal.

Row 2—Emptying of similar meal with duodenal tube in place. Illustrates the failure of tube through pylorus to significantly alter gastric emptying.

Row 3—Tap water when given by mouth leaves the stomach at a rate not noticeably different from that of an isotonic solution. This is due to the fact that such a meal rapidly becomes isotonic in the stomach. Water dripped into the duodenum at the rate of 80 drops per minute causes a definite delay in gastric evacuation because of its hypotonicity, it alters osmotic conditions sufficiently to stimulate the duodenal mechanism concerned with gastric evacuation.

Row 4—Normal saline into duodenum fails to change gastric evacuation.

Row 5—The same is true when 5 per cent glucose, a nearly isotonic solution, is instilled into the duodenum.

Row 6 and 7—When hypertonic solutions of either non-electrolytes such as glucose or electrolytes such sodium chloride are instilled into the duodenum—a very striking delay in gastric emptying occurs. The delay in evacuation varies as the degree of hypertonicity of the duodenal instillate.













| An Achlorhydric | | | | |
|---|---|---|---|-------------------------|
| 5 min | 15 min | 30 min | 60 min | |
|  |  |  |  | Standard Water Meal |
| Empty in 60 min. | | | | |
|  |  |  |  | 5.0% Sodium Chloride |
| 90% residue in 60 min. | | | | |
|  |  |  |  | 25.0% Olive Oil |
| 90% residue in 60 min | | | | |

Fig. 3. Illustrating the delay in gastric evacuation when the water of the meal orally administered (Row 1) is changed to 5 per cent sodium chloride (Row 2), and to a 25 per cent emulsion of olive oil (Row 3).

When normal gastric acid is present, the regular stimulation of the duodenal mechanism is assured. When gastric acid is absent, as in the achlorhydric, the intrinsic stimulus is missing and the normal rhythmicity of gastric emptying is lost when the ingested meal does not contain a suitable stimulus. Our studies¹ with various concentrations of sodium bicarbonate demonstrate the behavior of the duodenal mechanism under various conditions. An isotonic solution of sodium bicarbonate dripped into the duodenum will influence gastric emptying of a water-barium meal, depending upon the gastric acid response of the test subject. In an individual with gastric anacidity, gastric evacuation will be unaffected by the duodenal instillate. In one with normal gastric acidity, gastric evacuation will be hastened. This occurs because the duodenal instillation of an isotonic, or nearly isotonic, solution of sodium bicarbonate, while itself incapable of activating the duodenal mechanism, actually enhances the normal neutralizing apparatus of the duodenum, hastens neutralization of the gastric contents entering the duodenum, and hurries gastric evacuation. However, when the sodium bicarbonate instilled is hypertonic, gastric evacuation is delayed in all cases (Fig. 4).

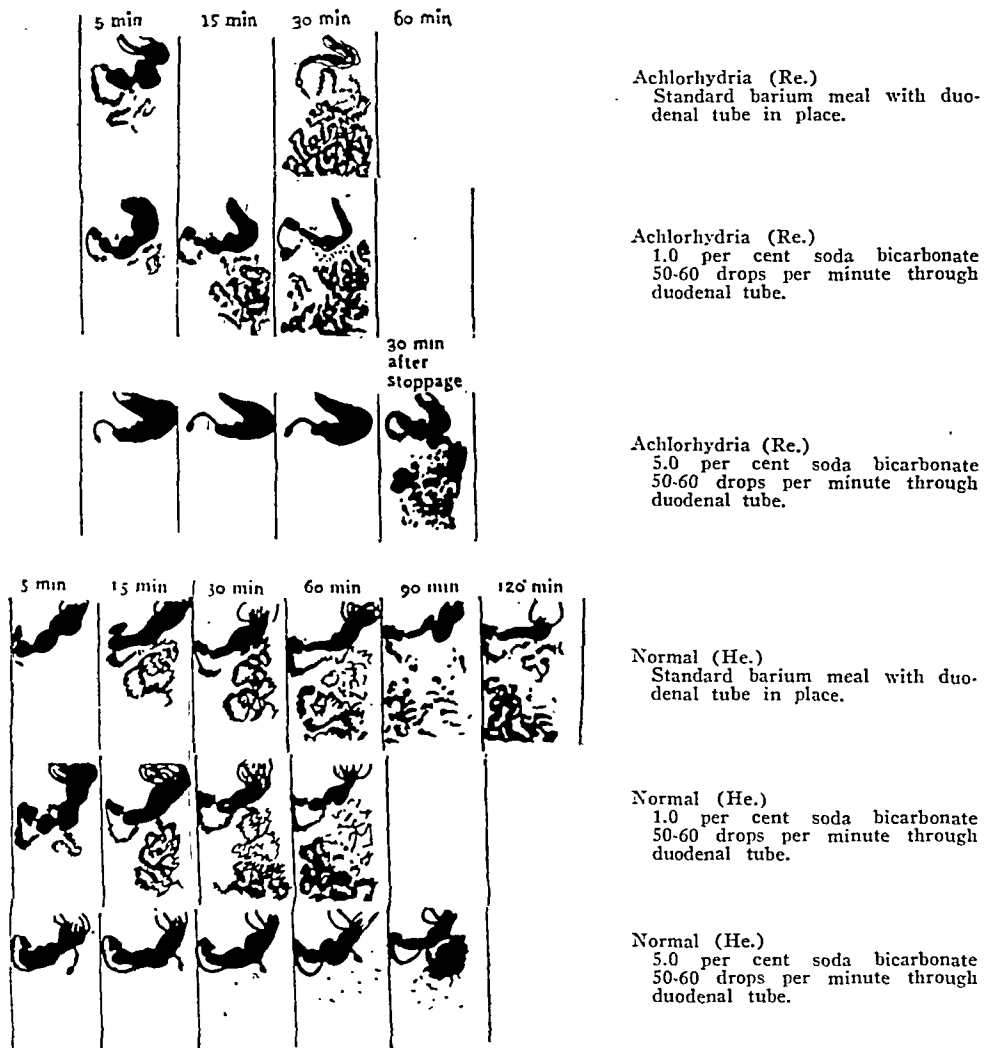


Fig. 4.

The effect upon gastric emptying of a sodium bicarbonate solution administered orally or intraduodenally depends upon the concentration of the solution and the type of gastric acid response of the individual. The duodenal instillation of a 1 per cent (nearly isotonic) solution of sodium bicarbonate in an achlorhydric subject (Row 2) does not change materially the gastric evacuation of the oral water and barium meal when compared with its emptying when nothing was instilled into the duodenum (Row 1). A 1 per cent sodium bicarbonate solution does not change osmotic conditions in the duodenum of an achlorhydric sufficiently to stimulate the duodenal mechanism described.

In an individual with a normal gastric acid response, the duodenal instillation of such a solution hastens gastric evacuation (See Rows 4 and 5), because the bicarbonate enhances the normal duodenal neutralizing mechanism and so more rapidly neutralizes the gastric acid mixture reaching it intermittently through the pylorus.

The duodenal instillation of hypertonic solutions of sodium bicarbonate cause a marked delay in gastric evacuation, whether the patient is an achlorhydric or has a normal gastric acid response (See Rows 3 and 6).

The following experiment besides illustrating this point, produces conditions which indicate the fallacy of the first part of the Cannon theory of gastric evacuation. Through a tube with its tip in the proximal duodenum we slowly instilled a 5 per cent solution of sodium bicarbonate. A 0.5 per cent hydrochloric acid solution containing barium sulphate was administered by mouth. Thus, while acidity on the gastric side of the pyloric sphincter and alkalinity on the duodenal side should have been ideal for gastric emptying from the standpoint of the Cannon theory, the merest traces of barium sulphate were seen to pass the pylorus during the two hour period of observation.

In our roentgen studies in the human subject we were especially impressed with the closure of the pylorus as a result of duodenal stimulation. However, gastric peristalsis and tonus were also decreased. We have pictured our concept of the local mechanism concerned in gastric evacuation in a simple simile: "The stomach is like a dumbwaiter ever ready to deliver through its door, the pylorus, anything reaching it. The duodenum, however, sensitive connoisseur, is selective. If the gastric contents are acceptable to the official taster, the duodenal cap, gastric emptying continues uninterruptedly; if not, the door, or pylorus, is hurriedly closed and stays so until the portion stated, 'trial portion,' is rendered acceptable." Quigley³ although stressing antral peristalsis rather than pyloric action, wrote recently concerning gastric evacuation: "According to recent observations made in this laboratory, the normal course of events proceeds according to the following pattern:— A small portion of gastric contents enters the intestine. If the sample proves satisfactory, the remainder leaves the stomach rapidly; unsuitable material initiates reactions from the duodenum which temporarily retard further gastric evacuation." Thus for the major premise as it concerns our thesis for this evening, there is agreement in our findings in man with those obtained by the physiologist in dogs.

Duodenal Ulcer and Altered Gastric Motor Function: The most sensitive part of the duodenal mechanism described above is lodged in the duodenal cap. Although gastric motor function may be influenced by stimulation of the intestine beyond the cap, the sensitivity of the mechanism decreases rapidly beyond this point. In view of these findings, the clinical fact that duodenal ulcer occurs in the cap in at least 95 per cent of cases becomes especially pertinent. With the development of the ulcerative process in this area and the associated duodenitis

in adjacent portions of the duodenum, the duodenal mechanism concerned with gastric motor delay becomes impaired. Stimuli reaching the duodenum which would activate this mechanism fail to do so as readily as under normal conditions. The normal brake not acting efficiently, gastric peristalsis, tonus and gastric evacuation are exaggerated, resulting in the hyperperistalsis, hypertonicity and rapid gastric evacuation seen so frequently in uncomplicated duodenal ulcer.⁵ It is important to emphasize that the duodenal mechanism is dulled only and not destroyed, because when healing of the ulcer occurs, the response of this mechanism may, and often does, become normal.

Gastric Secretion in Gastric and Duodenal Ulcer: Before discussing gastric secretion, I should like to devote a moment to a consideration of the ulcer terminology. The term "peptic ulcer" to denote both gastric and duodenal ulcer is an unfortunate one, I believe, because it makes us think of gastric and duodenal ulcers, not only as derivatives of an identical cause, but also as the producers of changes in the same physiological mechanisms. Although by definition, peptic ulcer permits grouping of gastric and duodenal ulcers, and even though pathologically both are ulcerative processes, they are quite distinct diseases in their effects on physiological mechanisms. I do not believe that physiological studies carried out in gastric ulcers should or can be applied to duodenal ulcers or vice versa. As a matter of fact it is on this basis that some of the differences of opinion in the literature can be easily understood. In general, the subject would benefit if the term "peptic ulcer" were dropped and the lesions referred to anatomically.

Hyperacidity is another clinical term for which there is no real basis, since the definitive results of Hollander⁶ clearly settled the Pavlov-Rosemann Theories' controversy to establish finally that the concentration of acid in the parietal secretion does remain constant. The clinical measurement of acidity by gastric analysis measures not the acid as secreted by the parietal cells, but measures the end result of several factors—rate of acid secretion, dilution and neutralization by test meal, mucus, dilution fluid, duodenal regurgitation and also, in the case of clinical test meals, the rate of gastric emptying.

Gastric ulcer does not show a typical gastric acidity. The secretory picture, in the aggregate, is very nearly normal; however, individual gastric secretory responses, as measured by fractional gastric analysis, do vary over a wide range. This is in contrast to the usual type of gas-

tric acidity curve obtained in uncomplicated duodenal ulcer under similar conditions. The wide variation in acidities found in gastric ulcer is very probably dependent upon the location of the gastric lesion and upon the character and amount of associated gastritis. Ihre,⁷ from gastric secretory studies in a large clinical material, was among the first to point out the normal rate of secretion in gastric ulcer and the hypersecretion, often marked, that occurs in duodenal ulcer. He found also that chronic gastritis without ulcer showed a clear tendency towards hyposecretion. Since there is a variable degree of gastritis associated with gastric ulcer, the interplay of reactions resulting from the location of the ulcer and the gastritis, together with the type of local response activated in the secretory cells by the pathology (ulcer destructive, gastritis-depressing), would account in good measure for the variety in acid response found in fractional gastric analyses in this disease. Support for this viewpoint may be found in the data of Vanzant, Alvarez, Berkson and Eusterman.⁸ They found, from a statistical analysis of their results, that gastric acidity was below the normal level in gastric ulcer. They found a slightly greater reduction in acidity with larger ulcers (over 5 mm. dia.). Of especial interest were their findings that ulcers at, or near, the pylorus were associated with acid values not significantly different from the normal. Ulcers in the middle third of the stomach showed a reduction in acidity, while those in the upper third showed the greatest acid reduction. Differences in size could not account for a large portion of the acid producing area, therefore, only slight differences in acidity were disclosed in the data of Vanzant et al⁸ dealing with this aspect of ulcers. Ulcers and associated gastritis situated in the pyloric portion of the stomach, the area whose normal secretion is alkaline, lead to no destruction or depression of acid secretory cells. Although the secretion of this portion of the stomach (containing none or only a very few parietal cells)⁹ is alkaline, the rate of pyloric secretion is so low that a destructive lesion in the pyloric area appears to be unimportant to a direct control of the gastric acid picture. Apparently the pyloric mechanisms concerned with the control of the so-called second or pyloric phase of gastric secretion,¹⁰ and with the production of the agent isolated from the pyloric mucosa by Komarov¹¹ which produces a high acid, low pepsin juice on intravenous injection, are not seriously impaired. This is in accord with clinical experience. The clinical observation reported by Bockus¹² that the acid titer in persons with

ulcer in the pyloric canal probably does not differ from that found in duodenal ulcer patients may have as its explanation a disturbance of the duodenal mechanism to be described under duodenal ulcer. It may result from the extension of the irritation beyond the pyloric ring producing a duodenitis and a depression of the duodenal mechanism concerned with the control of gastric secretion.

If the lesions are situated in the corporic or fundic portions of the stomach, acid producing areas are destroyed and depressed, depending on the total area involved by the ulcer and the associated gastritis. There is also evidence that local damage to the vagi may be an important contributory factor to the production of the gastric secretory depression.

Although generally it is believed that the parietal cells are distributed nearly uniformly in the body and fundus, the greater depression of acidity seen by Vanzant et al⁸ in fundic over corporic ulcers, suggests the possibility of a richer distribution of parietal cells in the more cephalically located portions of the stomach.

Schiffrin and Ivy¹³ in a very recent publication discussing the physiology of gastric secretion particularly as related to ulcers, commented on the hypersecretion in duodenal ulcer uniformly reported. They stated that there is no satisfactory explanation of this phenomenon. We believe our data⁵ do permit a satisfactory explanation, because they account not only for a part of the mechanism concerned with the normal gastric acid curve, but also allow an interpretation of the altered curve in uncomplicated duodenal ulcer as well as a fuller understanding of the beneficial effects produced by the chief constituents of the ulcer diet.

To avoid any misinterpretation, let me emphasize that I am not suggesting that any type of gastric secretory curve is to be considered diagnostic of any disease. Nevertheless, the hypersecretory curve of gastric acidity continually rising until the stomach is empty of the test meal (Fig. 5, Curve 2), occurs so frequently in uncomplicated duodenal ulcer that the need for its explanation becomes imperative if we are to complete the picture of the altered gastric function.

Bockus, Glassmire and Bank¹⁴ reviewed their results of fractional gastric analysis in 200 patients with duodenal ulcer and found an acidity that was higher than normal. Vanzant et al⁸ from a statistical analysis of their data reported similar results although their observations were based on a single one-hour extraction after an Ewald type

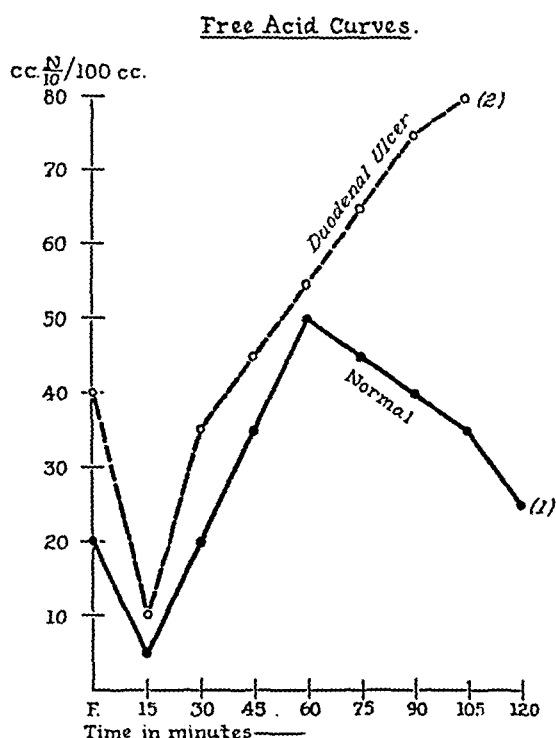


Figure 5

meal. Their results showed a mean acidity increase over normal of 12.3 units in men and 11.5 units in women. If the peak acidities of the usual continually rising type of fractional gastric acid curve had been recorded and analyzed, I believe these differences would have been even greater.

In order to attempt an explanation of the mechanism responsible for the type of gastric acid curve so frequently obtained in uncomplicated duodenal ulcer, we will first have to consider the mechanisms responsible for the gastric acid curve seen in the normal individual in response to an Ewald type test meal.

The fasting gastric contents of a normal person will show a free acidity of approximately twenty clinical units. When an Ewald type meal is administered and extractions made at fifteen-minute intervals, the acid curve usually presents the following pattern: The first fifteen-minute extraction on titration will show an apparent drop in acidity as compared with the fasting sample. This drop is only apparent and is dependent upon the dilution of the gastric contents by the test meal. This may be proven by the use of a dilution indicator.¹⁵ After

Free Hydrochloric Acid Curves.

—Normal—

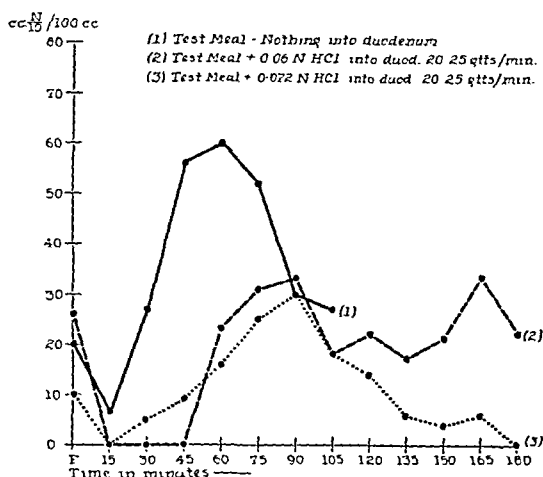


Fig. 6

For this and subsequent illustrations of gastric acid response, the following technique was used:

The patient, after an overnight fast, was intubated with two Rehfuß tubes. The tip of one was allowed to enter the duodenum and advance to the proximal portion of the second duodenal segment by the usual technique. The tip of the second tube was allowed to reach the most dependent portion of the stomach. The tube tips were located fluoroscopically and the tubes were fixed with adhesive about the mouth.

Curve 1—Ewald type test meal administered orally, nothing introduced into duodenum. Peak free acidity reach—60 cc. N/10 HCl per 100 cc. gastric juice (60 clinical units).

Curve 2—Free acid curve when similar test meal was given and HCl 0.06N (60 cc. N/10 HCl per 100 cc.) was dripped into duodenum at rate of 20-25 drops per minute. Note the marked depression of the gastric acidity curve under these conditions.

Curve 3—Experimental depression of the gastric acidity curve under these conditions. Curves 2 and 3 show the effect upon gastric motility as well as upon acidity—the result of stimulation of the duodenal mechanisms concerned with these gastric functions by the acid solution in the duodenum.

the first fifteen-minute extraction the acidity rises and reaches a peak at sixty to seventy-five minutes of 40 to 60 clinical units. From this point the curve takes a downward course until the stomach is empty which is usually at the end of two hours for the Ewald type meal. At this point the acidity has approximated the fasting level (Fig. 5, Curve 1).

The rising limb of the gastric secretory curve can be explained by the combined action of the cephalic and pyloric mechanisms of secretion as well as the diminishing effect of dilution by the test meal. The descending limb is, we believe, dependent upon a mechanism that is located beyond the pylorus. We base this belief upon the following evidence: If in an individual with a normal gastric acid curve

after an Ewald meal, hydrochloric acid of a concentration represented by the peak gastric acidity reached in response to that meal is dripped slowly into his proximal duodenum, the gastric acid response to a similar meal administered simultaneously will be markedly depressed (Fig. 6). Recently Friedman, Pincus and Thomas¹⁶ in Pavlov pouch dogs found that the intraduodenal instillation of hydrochloric acid inhibits gastric secretion in response to a meal if a threshold level of duodenal pH is attained. Particularly relevant to our concept is their finding that the threshold level of intestinal pH for inhibition of gastric secretion is within the pH range of the antral contents. These results, we believe, prove that the duodenum in both dog and man houses a mechanism which when activated can cause a depression of gastric acidity. Further, this mechanism can be activated by an acid reaction in the proximal duodenum and this reaction can be produced by the gastric acid reaching the duodenum. In the individual with a normal duodenum, the activation of this mechanism occurs with the entrance into the duodenum of the peak gastric acidity reached for the test meal employed and accounts for the downward limb of the gastric curve seen in the normal fractional gastric analysis. The threshold of response of this mechanism determines, we believe, in a large measure, the type of gastric acid curve the individual will show. Thus, if the duodenal mechanism is activated by a duodenal pH produced by a gastric free acidity of 40 to 60 clinical units, a normal gastric acid curve will result. However, if the threshold of response of the duodenal mechanism is lower and responds at a higher pH, (lower acidity), gastric secretory depression will occur more readily and a low gastric acid response to the test meal will result. On the other hand, a duodenal mechanism with a higher than normal threshold of response, one requiring a lower duodenal pH (higher acidity) to activate it, will not react until the gastric acid has reached a peak which is higher than normal response and that individual will show a hypersecretory gastric acid curve. In the variations of the threshold of response of this duodenal mechanism lies the explanation for the isosecretory, hyposecretory and hypersecretory gastric acid responses of normal persons.

In duodenal ulcer, the lesion situated almost invariably in the cap, the location of the most sensitive part of the duodenal mechanism concerned with gastric secretion, impairs the activity of the mech-

Free Hydrochloric Acid Curves.

—Duodenal Ulcer—

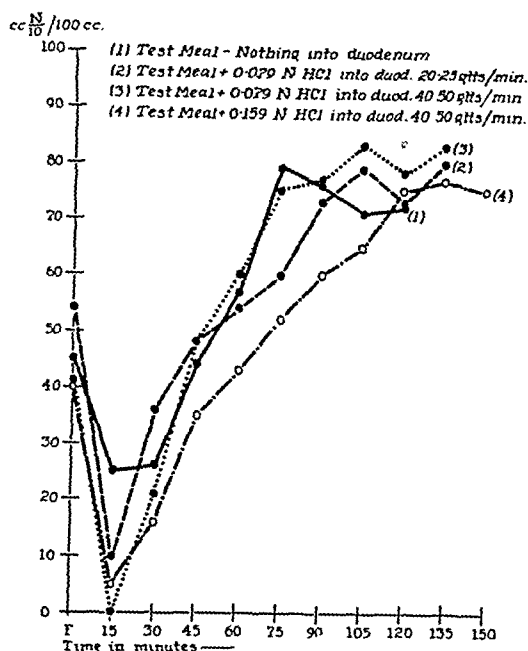


Fig. 7

Experimental conditions the same as for Fig. 6. Illustrates the continually rising type of gastric acid curve usually seen in uncomplicated duodenal ulcer (Extragastric type). It shows the failure of the duodenal mechanisms concerned with gastric motility and secretion to respond to acid representing the peak acidity reached by the patient in response to the test meal. The duodenal mechanisms are so obtunded that they fail to respond to acid instillation of increased concentrations (Curve 4).

anism to such a degree that with an Ewald type meal, the peak gastric acidity reached is usually inadequate to activate the obtunded duodenal mechanism. This is shown in Fig. 7. Such a concept would explain the results of Vanzant et al. who found that smaller or single duodenal lesions caused a lower increase in gastric acidity than did larger or multiple ones. Large or multiple lesions not only involve more of the duodenal mucosa but the associated duodenitis would be greater resulting in an involvement of more of the mechanism concerned with gastric secretion. That the mechanism is dulled and not destroyed is shown by the fact that with healing, gastric acid response can return to normal (Fig. 8). The tendency for gastric acidity to moderate in

Patient-HA (D.U.)

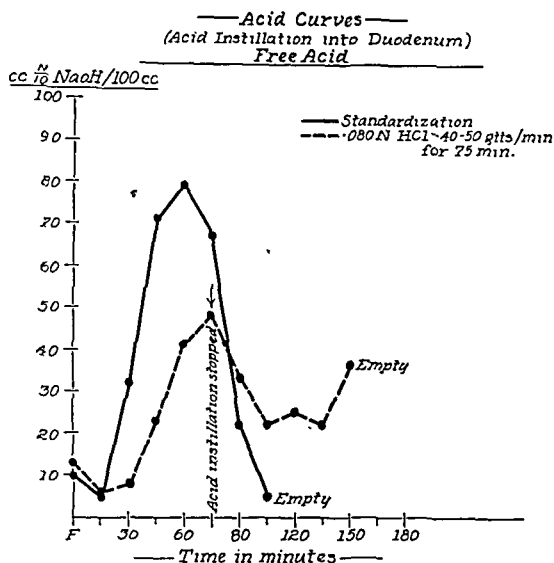


Fig. 8. Recovery of the duodenal mechanisms when ulcer healing had occurred. Same patient as in Fig. 7. Results obtained when patient had been entirely symptom free for a period of ten months. Although the peak acidity reached was not different from that seen during period of ulcer activity (Fig. 7), the type of curve had returned to normal and we could see a return of response of the duodenal mechanisms concerned both with gastric motor and secretory function.

duodenal ulcer as the gastrointestinal tract returns to normal has been reported by Brown and Dolkart.¹⁷ Hurst¹⁸ expressed the opinion that the characteristic x-ray findings of a hypertonic rapidly emptying stomach in duodenal ulcer and the hypersecretory hyperchlorhydric gastric curves reported by Crohn¹⁹ were not due to the ulcer because the same phenomena could be observed after the ulcer had healed. Before accepting this view, the question of when is a duodenal ulcer healed is not impertinent, because I believe there are no reliable clinical criteria upon which such an opinion can be based. The relief of symptoms or changes in the duodenal deformity roentgenographically cannot be accepted as conclusive evidence of healing. A return of normal gastric motor and secretory functions indicates healing of the ulcer because this expresses a restoration of normal function to the proximal duodenum. If this is true, then the corollary is that a failure to restore such function is an indictment of the medical management genuinely to heal duodenal ulcer. The high incidence of recurrences

in duodenal ulcer does not make such an indictment unreasonable. The major cause for such failure is that thus far a direct attack on the disturbed physiology has not been possible. Whether there is a distinct ulcer preventive factor as the work of Sandweiss and his associates²⁰ suggest, has not yet been confirmed.

The results we obtained have led to the belief in our laboratory that the increased gastric acidity stands in a consequential and not in a causal relationship to the initial duodenal lesion. The development of the duodenal ulcer interferes with the normal duodenal mechanism that is concerned with the control of gastric acidity—the normal brake impaired, gastric acidity increases. This would also explain the failure of Brown and Dolkart¹⁷ to observe any significant trend in the gastric acidity prior to a recurrence of ulcer activity. If the duodenal ulcer had not been previously healed to a degree which had permitted the duodenal mechanism to function, the acidity would, naturally, be increased during the remission, as well as during the attack. If prior to the attack there had been sufficient healing to permit proper functioning of the duodenal mechanism, gastric acidity could have returned to a normal pattern but would not have shown a change until the breakdown of the duodenal lesion had again impaired the duodenal mechanism. Our results lend significance to the isolated report of Lino.²¹ After producing a lesion of the duodenal mucosa by abrasion, Lino found an increased gastric acid response to a test meal. The acidity increased to the 5th or 6th day postoperatively and then rapidly diminished to return to normal by the 8th or 9th day. Because of the autopsy results on his animal, Lino related the period of hyperacidity to the presence of the duodenal lesion, while the return to normal gastric acidity was associated with healing of the duodenal abrasion. Berk, Reh fuss and Thomas²² have found that the contents of the duodenal bulb are more acid in patients with duodenal ulcer than in normal subjects. The rapid emptying of a hypersecreting stomach resulting from the altered duodenal mechanisms in duodenal ulcer could contribute much to the production of their findings.

We are in complete accord with Schiffrin and Ivy¹³ who do not believe that gastric acidity can cause duodenal ulcer but do ascribe to the action of the acid and pepsin an important role in the chronicity of ulcer. In this connection, due emphasis must be placed upon the pepsin whose maximum activity is dependent upon an optimum pH,

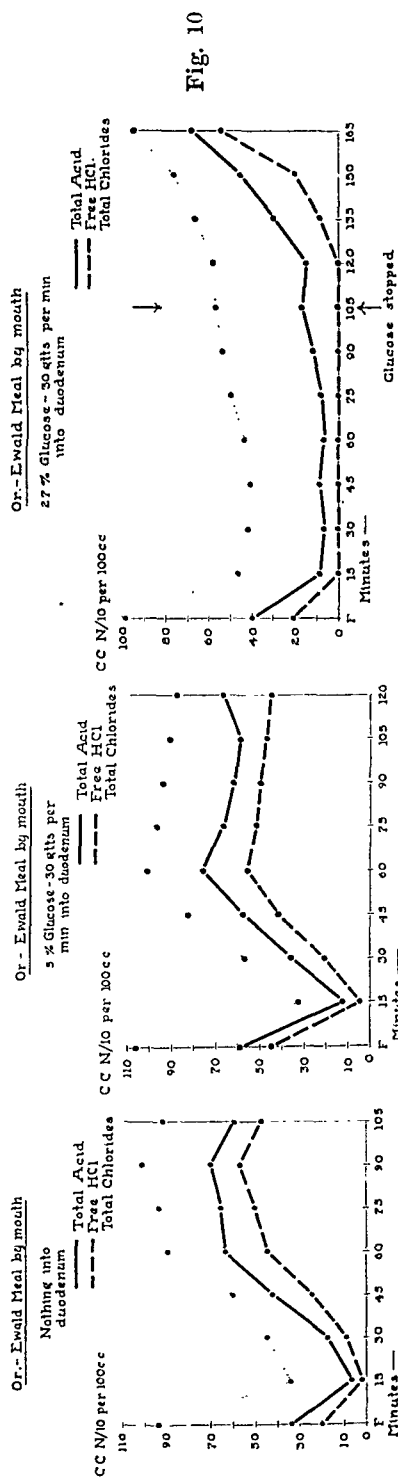
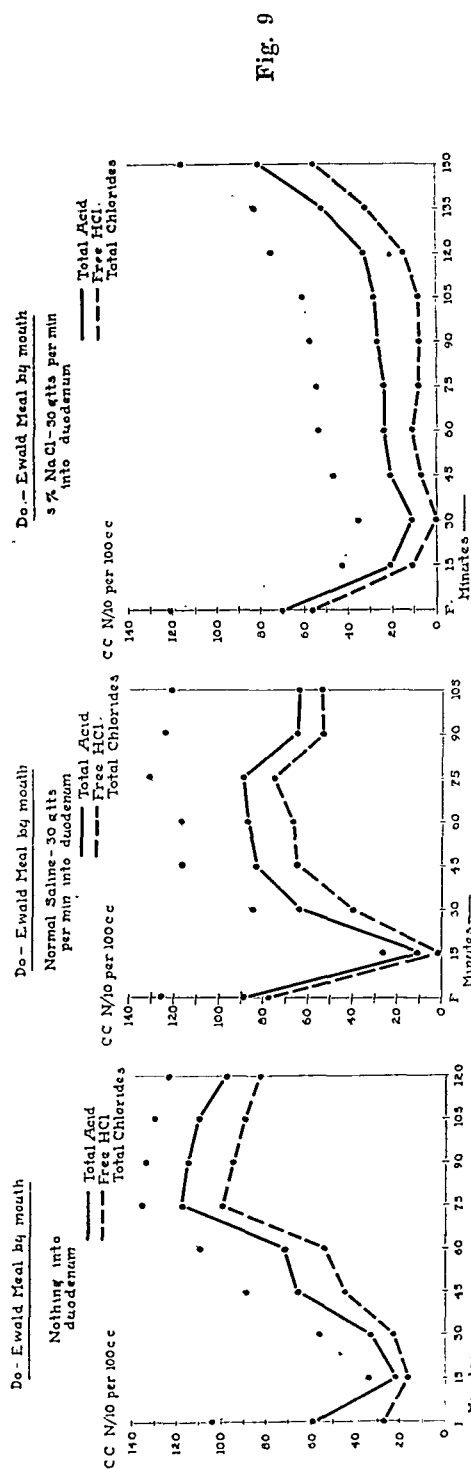


Fig. 9 shows the effect of alterations in osmotic conditions in duodenum upon gastric acidity. Isotonic solutions of electrolytes incapable of chemically activating the duodenal mechanisms, fail to influence gastric motor or secretory functions. Hypertonic solutions, however, stimulate these mechanisms very actively.

Fig. 10. The effect of solutions of non-electrolytes. Illustrates the influence that ingested foods may have upon gastric motility and secretion, aside from their intragastric effects, if they reach the duodenum in proper concentrations.

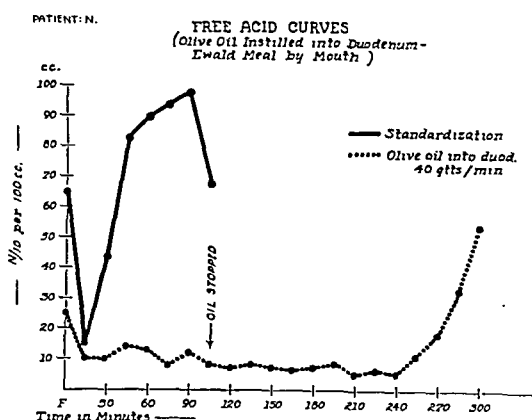


Fig. 11

The striking effect produced by the duodenal instillation of oil. Oil and cream may be effective in stimulating the duodenal mechanisms even during the active stage of duodenal ulcer. Oil instillation started with the ingestion of the Ewald type meal.

which in turn is dependent upon an adequate amount of hydrochloric acid. Schiffrin²³ has demonstrated the difference in the irritating properties of acid and acid pepsin by the perfusion of jejunal loops. Perfusion with acid pepsin solution always caused ulceration, while hydrochloric acid solution alone causes some destruction of the villi but without ulceration.

Like the duodenal mechanism concerned with the control of gastric emptying, the mechanism involved in gastric secretion is not activated solely by the gastric hydrochloric acid. Foodstuffs and other substances that reach the duodenum which have the proper chemical or physico-chemical effect may do so as well.²⁴ Thus hypertonic solutions of electrolytes (Fig. 9) and non-electrolytes (Fig. 10), and especially fats (Fig. 11) are effective.

In our studies we²⁴ succeeded in showing that the major, if not the sole, action resulting from the stimulation of the duodenal mechanism was an inhibition of the nervous phase of gastric secretion since we were able to inhibit the gastric secretory response incident to the hypoglycemia produced by insulin (Fig. 12). Direct stimulation of the parietal cells appears to be unaffected by the activity of the duodenal mechanism. This was shown when duodenal stimulation failed to prevent a rise in gastric acidity after histamine was injected (Fig 12).

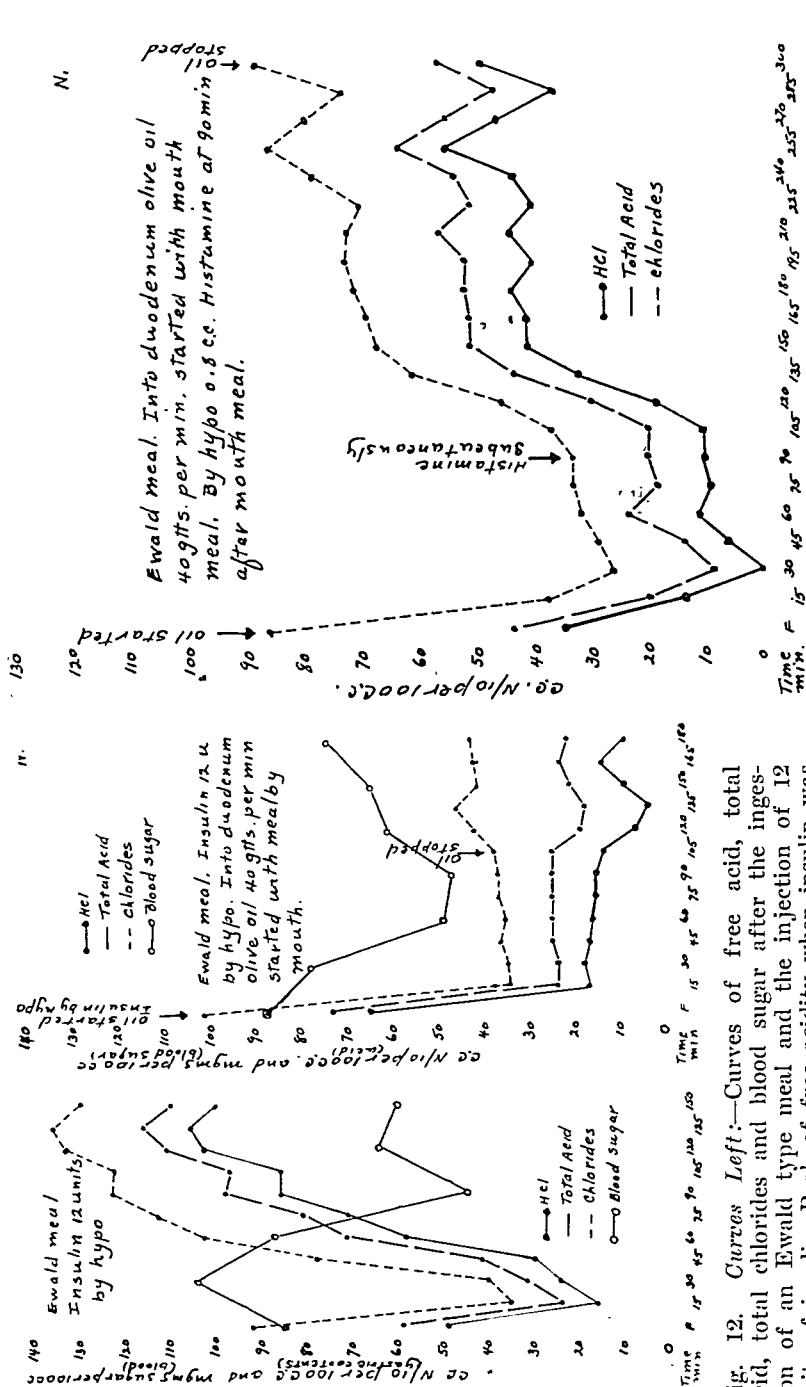


Fig. 12. *Curves Left*.—Curves of free acid, total acid, total chlorides and blood sugar after the ingestion of an Ewald type meal and the injection of 12 units of insulin. Peak of free acidity when insulin was not given was 80 clinical units.

Curves Center.—Response of same individual under similar experimental conditions, when olive oil was instilled into the duodenum, started when the Ewald meal was taken.

Since it is established that the stimulation of gastric secretion by insulin is a central vagus effect incident to the hypoglycemia produced, the inhibition of the gastric secretion by the oil in the duodenum shows that stimulation of the duodenal mechanism described, influences the nervous or first phase of gastric secretion.

Curves Right.—Ewald meal given, olive oil instilled into duodenum. After 90 minutes when the duodenal effect of the oil on the gastric acid curve was clearly established, histamine 0.1 mg. per 10 kilo of body weight was injected subcutaneously. Even though the duodenal instillation of the oil was continued, a sharp rise in gastric acidity soon occurred. Direct stimulation of the parietal cell, an effect which histamine action represents, is therefore not prevented by stimulating the duodenal mechanism.

Since vagal secretion is rich in pepsin, an impairment of the duodenal control mechanism would explain the hyperpepsinia as well as the hyperacidity reported in duodenal ulcer by Ihre.⁷

In the rather extensive literature on gastric secretion during sleep, all observers agree that during heavy sleep secretion is practically in abeyance in normal people but Winkelstein²⁵ found in duodenal ulcer cases that free secretion continued throughout the night. This was confirmed by Henning and Norpoth.²⁶ Considering these findings it is pertinent that Day and Webster²⁷ were able to demonstrate in dogs that gastric secretion, stimulated through the parasympathetic nervous system or by the presence in the intestine of food substances and products of their disintegration, is inhibited by the introduction of hydrochloric acid into the duodenum. An impairment of this duodenal mechanism could, therefore, explain the frequent clinical observation of a high interdigestive secretion in duodenal ulcer. It would explain also the high basal secretion reported by Bloomfield, Chen and French²⁸ as well as their failure to find such increased secretion in gastric ulcer.

The *modus operandi* of the duodenal mechanisms for gastric motor and secretory functions we are not prepared to state. There is evidence that both nervous and humoral mechanisms are involved. If the action is dependent upon the production of enterogastrone we do not know, although Gray, Bradley, and Ivy²⁹ have shown that enterogastrone containing preparations extracted from the upper intestine, inhibits both gastric motility and secretion. Our results in the human being differ from those of Gray et al in that they found that their extract was effective in inhibiting the secretory response of dogs with pouches to histamine. We were unable to check histamine secretion in the human subject by stimulating the duodenal mechanism. Friedman, Pincus and Thomas¹⁶ were able to confirm in Pavlov pouch dogs that insulin-provoked secretion is inhibited by an adequately acid duodenal content, but that histamine-provoked secretion is not.

The duodenal mechanisms concerned with gastric motor and secretory functions react at different levels of stimulation. The one concerned with gastric motor function responds at a lower level than does the one which influences gastric secretion. This illustrates nature's logical procedure, because it is desirable at the beginning of a meal that gastric emptying be slowed to allow for proper gastric mixture and digestion, while gastric secretion should be depressed later only



























| R.A. NORMAL SUBJECT NORMAL SECRETORY RESPONSE | 5 min. | 15 min. | 30 min. | 60 min. | 90 min. |
|--|---|--|---|--|--|
| Standard water-barium meal 250 c.c. water 2 ounces barium sulphate |  |  | |  |  |
| Milk-barium meal 250 c.c. AA milk 2 ounces barium sulphate |  |  |  |  |  |
| Cream-barium meal 250 c.c. table cream 2 ounces barium sulphate |  |  |  |  |  |
| Standard water-barium meal with duodenal tube in place |  |  | |  |  |
| Milk—30 drops per minute through duodenal tube Standard water-barium meal by mouth |  |  |  |  |  |
| Cream—6 to 10 drops per minute through duodenal tube Standard water-barium meal by mouth |  | |  | |  |

Fig. 13

Striking inhibition of gastric emptying produced by milk and cream. Rows 5 and 6 show this effect to be due to the action of these substances in the duodenum.

when these have been accomplished.

Having considered the mechanisms involved in the production of the disordered gastric motor and secretory function in gastric and duodenal ulcer, it may not be amiss to consider briefly how these disturbed functions are altered by ulcer therapy. Milk and cream have been and remain the mainstays of the ulcer diet. Data have gradually

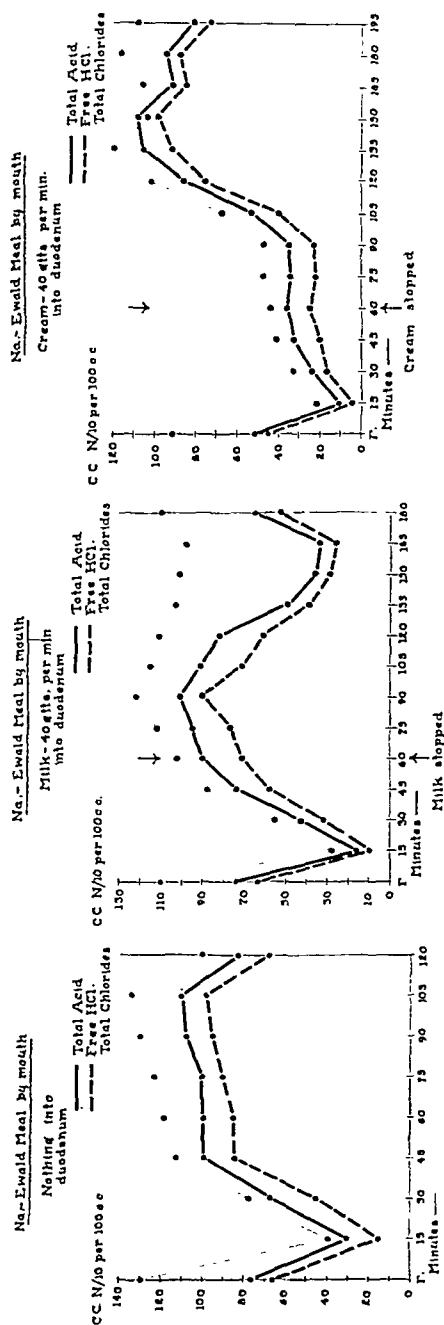


Fig. 14

The center curves show that milk in the duodenum depresses gastric evacuation but does not appreciably influence the gastric acid curve. The duodenal instillation of cream, however, stimulates both duodenal mechanisms, the one concerned with gastric secretion, as well as that which influences gastric evacuation. The effects of milk and cream (Figs. 13 and 14) may be obtained in patients with active duodenal ulcer. In this action, we believe, rests an important part of the major role maintained by milk and cream in the ulcer diet.

accumulated to show why this should be. If gastric hydrochloric acid and pepsin are important in the chronicity of ulcer, neutralization of acid and binding of pepsin become of paramount importance. For this purpose milk is an ideal food; its protein will bind pepsin and its buffer action in neutralizing acidity has been amply demonstrated.³⁰ Milk has the further advantage that as a gastric stimulant it calls forth

a very low rate of gastric secretion with the lowest acid and pepsin values in comparison with other common foods.³¹ When to these effects is added the action of fat in the duodenum,³² the special value of cream becomes evident (Figs. 13 and 14). In the difference of the effect of milk and cream upon the motor and secretory functions of the stomach may also be seen what is meant by the difference in threshold of response of the duodenal mechanisms concerned with gastric motor and secretory functions. I have already pointed out that the duodenal mechanisms concerned with gastric motor and secretory functions are dulled, *not* destroyed, in most instances in duodenal ulcer. It is true also that the action of fats is more effective than that of gastric acid in stimulating these mechanisms—we have been able to produce a response by fats in ulcer patients when acid failed.³³ In this action lies an important part of the beneficial value of milk and cream and fat to the ulcer diet. It may be, too, that those uncomplicated duodenal ulcer patients who fail to respond to a medical regime may represent cases of duodenal mechanisms which have been so damaged that they fail to react even to fat. In these cases the diet and medication would be unable to restore normal gastric function even in part and thus fail to relieve the subjective symptoms of pain and distress which are manifestations of the disordered gastric physiology.

SUMMARY

1. Gastric and duodenal ulcers produce changes in gastric motor and secretory functions.
2. The changes caused by the former can be related to the action of the lesion upon local gastric mechanisms.
3. The changes in gastric function produced by duodenal ulcer, we believe, we have demonstrated to be due to damage of duodenal mechanisms, whose activities are concerned with decreasing gastric evacuation and secretion.
4. The most sensitive portion of these duodenal mechanisms is located in the cap, the usual site of duodenal ulcer.
5. As a rule, the mechanisms are obtunded and not destroyed by the ulcer and may recover with healing of the lesion. A return of gastric motor and secretory function to normal, we offer as probably the only reliable criteria of healing of a duodenal ulcer.
6. Though obtunded by the ulcer and associated duodenitis, the duo-

denal mechanisms in most cases of active ulcer can still respond to stimulation by fat. Upon this fact, rests part of the therapeutic value of milk and cream in the ulcer diet.

7. An impairment of the duodenal mechanisms to a degree where they can not react even to fat stimulation may account for those uncomplicated duodenal ulcers that fail to respond to a medical regime.
8. The duodenal mechanism concerned with gastric secretion, we believe, is largely responsible for the diminishing gastric acidity seen in the second half of a normal fractional gastric analysis and is an expression of the self-regulatory mechanism of gastric secretion.
9. The term "peptic ulcer" is an undesirable one because gastric and duodenal ulcers are not derivatives of the same cause and in their effects upon gastric physiological mechanisms they are different diseases, in spite of the fact that they are both ulcerative processes.

I am aware that I have not discussed other mechanisms that may influence gastric motor and secretory functions. I thought I could perhaps be most useful, if I were to crystallize for you what we have learned about the local gastric motor and secretory mechanisms from their study directly in the human subject and how that information might be used to explain the manifestations of disordered gastric function with which we as clinicians are constantly confronted in the management of patients with gastric and duodenal ulcer.

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PRIMARY ATYPICAL PNEUMONIA IN GENERAL HOSPITALS AND IN PRIVATE PRACTICE *

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and

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THE reports on primary atypical pneumonia of unknown etiology or so-called "virus-type pneumonia" that have appeared in increasing numbers during the past five years have described this disease as it has occurred among special groups of individuals such as in colleges,^{1, 2} army camps,^{3, 4} and among medical and nursing personnel of hospitals,⁵ but very little has been written about its occurrence in general hospitals or in private practice. The explanation for this is clear. Primary atypical pneumonia of unknown etiology as seen in college infirmaries or in army and navy station hospitals stands out as a well-defined disease entity, whereas in general hospitals and in private practice with patients of all ages included, the cases of primary atypical pneumonia are intermixed with such a variety of other respiratory cases that it is difficult to visualize the disease in its pure form. The clinical diagnosis of primary atypical pneumonia in private practice and in general hospitals usually is difficult and sometimes impossible, whereas in the special groups mentioned the diagnosis is obvious even in the early stage of the disease.

Our experience with pneumonia started at Bellevue Hospital, where nearly all of the pneumonias were proved bacterial infections and where we saw only an occasional primary atypical pneumonia, although in retrospect we believe that each year there were some atypical cases, particularly among the late summer and early fall pneumonias that were milder and gave an unsatisfactory pneumococcal typing. Next, we had experience at The New York Hospital and in private practice

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in New York City, where we observed more of the primary atypical cases. Since the introduction of sulfapyridine a large part of the consulting pneumonia practice in New York City has dealt with the primary atypical disease. Finally, during last fall and winter (1942-1943) we were given the opportunity to follow and study 205 pneumonia patients hospitalized in the Cornell University Infirmary in Ithaca, N. Y., of whom 196 were adjudged to have the primary atypical variety. This last experience gave us our first picture of the disease in its almost unadulterated form and furnished us a basis for comparison with our earlier experiences with pneumonia.

Fortunately, the clinician now is attaining a clearer conception of the different etiological varieties of pneumonia. We know now that in addition to the recognized bacterial pneumonias (pneumococcal, streptococcal, staphylococcal, etc.) there are also, but much more rarely, rickettsial pneumonias (typhus, Rocky Mountain spotted fever, and Australian and American Q fever) and true virus pneumonias (psittacosis, ornithosis, and possibly influenza and others). In addition, there is a pneumonia that has many clinical resemblances to the proven rickettsial and virus pneumonia which we now designate as primary atypical pneumonia, etiology unknown.

Until recently this disease was designated by a different name in almost every report dealing with it. The following list shows the maze of terminology that was used:

Virus pneumonia

Virus-type pneumonia

Primary virus pneumonitis

Interstitial virus pneumonia

Interstitial virus pneumonitis

Acute interstitial pneumonia (pneumonitis)

Acute interstitial pneumonitis

Pneumonitis

Acute pneumonitis

Simple pneumonitis

Atypical pneumonia
Primary atypical pneumonia
Atypical pneumonitis
Atypical pneumonia with leukopenia

Atypical bronchopneumonia of unknown etiology
Bronchopneumonia in adolescence
Bronchopneumonia of unknown etiology
Bronchopneumonia of unknown etiology (variety X)

Acute influenzal pneumonitis
Acute influenzal pneumonia

Disseminated focal pneumonia
Benign broncho pulmonary inflammation associated with
transient radiographic shadows

Primary atypical pneumonia, etiology unknown

It can be seen that the tendency has been to use pathological as well as etiological terms. Still today the pathology as well as the etiology of this disease is almost completely unknown because of the few fatalities that have occurred from it. (Perhaps a better designation would be "primary atypical pneumonia, etiology *and* pathology unknown.") To call this disease influenzal pneumonia or influenzal pneumonitis is particularly misleading, because this terminology already is used to designate three other types of pneumonia: the 1918 variety which was rapidly fatal and probably a secondary bacterial infection following influenza, the pneumonia caused by the influenza bacillus or Pfeiffer's bacillus, and the true virus pneumonia caused by the influenza virus. Until more is known about the etiology and pathology of primary atypical pneumonia, a clinical terminology only should be used. It is even true that the disease may not be primarily a pneumonia, but a more general infection in which the pulmonary changes are only of secondary importance, such as in typhus or Q fever.

Atypical pneumonia, as we have observed it at the Cornell University Infirmary and as it has been described as occurring there² and in other colleges and in army camps, certainly seems to be a well defined

disease entity, and its incidence in special groups and also in general practice is relatively high. As in pneumococcal pneumonia, this pneumonia of unknown cause varies in its incidence from year to year. Last year (1942-43) its incidence was high; this year (up to the present) it has been much lower. Each year since this disease has been recognized, its prevalence has been high in the late summer and autumn and much lower in the winter and spring, the time when the incidence of pneumococcal pneumonia is the highest. We clinicians believe that this seasonal relationship should give the epidemiologists some clue to the mode of transmission of this type of pneumonia. This year another unusual phenomenon occurred which may offer some lead as to the origin of this disease. About November 20, when influenza A appeared in this section of the country, primary atypical pneumonia almost entirely disappeared.

We believe it to be true that primary atypical pneumonia is occurring in every part of the United States, probably in every part of the world. Reports from our own army station hospitals have described cases in almost all parts of the U. S., as well as in the Hawaiian Islands, Panama Canal Zone, the South Pacific area, Europe, and North Africa. In civilian practice, primary atypical pneumonia is widespread and has become one of the more important medical diseases. Every hospital in New York City last year, and this year to a less extent, has seen a number of cases of this disease. Last year on the infectious disease service of The New York Hospital there were 29 cases of primary atypical pneumonia as compared with 47 of pneumococcal lobar pneumonia. In the entire hospital there were 52 cases during the year. The disease occurs at every age and in every walk of life. Our oldest patient at The New York Hospital was sixty-six and our youngest was four years of age. Persons in early adult life are apparently much more frequently afflicted, as evidenced by the high incidence of the disease in universities and in army and navy camps. The incidence among physicians and nurses is high. The medical departments of industrial organizations are diagnosing many mild cases of the disease by taking chest x-rays of employees who are returning to work after a number of days at home because of so-called "grippe" or a chest cold.

We call this disease atypical pneumonia. Nevertheless, it has a number of striking clinical characteristics and in some respects its course is more typical than that of lobar pneumonia. The onset is rarely sud-

den, such as that of the chill or the severe pleural pain of lobar pneumonia, but is gradual and frequently insidious. Fever, with associated chilly sensations, headache and generalized weakness, usually initiates this type of pneumonia. Because the fever is intermittent—and this is one of its chief characteristics—it is sometimes not discovered for several days. Shortly after the onset a dry, irritating cough commences, although some patients exhibit no cough throughout their illness while in others it is a very distressing symptom. Late in the disease the cough becomes productive of a small amount of mucopurulent sputum; but occasionally the expectoration is profuse. The sputum is almost never rusty and tenacious (so-called “pneumonic”); however, occasionally associated with severe coughing it may be slightly blood-streaked. The patient quite often complains of a slight to moderate soreness in the chest but almost never has real pleural pain. The appearance of the patient presents a striking contrast to that seen in pneumococcal pneumonia. At the time of day when the temperature is elevated, the skin may be moist and flushed, but only the severe cases show any degree of cyanosis or dyspnea. The average duration of fever is 9 days, but we have observed patients in whom it has persisted for more than 6 weeks and others in whom it lasted less than 24 hours.

The physical signs in primary atypical pneumonia usually are not very helpful in making the diagnosis. In a few early cases and in most of the late ones, rales can be heard over the affected lung but as a rule the signs are not sufficiently pronounced to present an accurate criterion of diagnosis. The breath sounds may be suppressed in the early stages. A few cases (less than 10 per cent) have signs of consolidation.

The x-ray findings have been more helpful than any other in accurately diagnosing and in shaping our present concept of primary atypical pneumonia. The earliest change is that of increase in the bronchovascular markings extending from the hilum, changes which sometimes can be made out only by having for comparison an earlier normal film. Soft homogeneous shadows develop later along these distended roots, and finally a fan-shaped density extends into the periphery. Occasionally either a homogeneous lobar shadow or a bronchopneumonic type of mottling, resembling a tuberculous infiltration, is found. In a few early cases the first x-ray was negative and was not positive until the third or fourth day of the disease. This is one of the evidences that suggests the disease is a generalized one; perhaps in only part of

the cases does it localize in the lung. At any rate, today it is impossible to diagnose this infection without a positive x-ray examination.

One of the most remarkable features of primary atypical pneumonia is the frequency with which all of the routine laboratory tests, other than the chest x-ray, are negative. One may see a patient with a temperature of 104°F. with extensive x-ray signs, and still the blood count, urine analysis, blood culture, sputum examination, throat culture, and even a variety of serological studies are all negative. The blood count early in the disease is usually within normal limits, except for possibly a slight increase in the young polymorphonuclear cells. During the later stages of infection the total white cell count usually is slightly elevated and we have occasionally seen, late in the disease, an elevation up to 25,000. The negative sputum examination and negative blood culture study are most important confirmatory findings in this disease. Careful and complete bacteriological studies always should be carried out in any severe case in which there is concern about the final outcome. Special virus studies, except in a few cases, have not been at all revealing. The identification of the causative agent of atypical pneumonia remains a most active field for investigation. Many reports have appeared but, except for a very few cases proven to be caused by known viruses or rickettsia, the disease as a whole continues to be of unknown etiology.

The serum of patients recovering from primary atypical pneumonia is positive for cold agglutinins in a high percentage of cases.⁶ Also in some patients the convalescent serum shows heterophile antibody. Recently Horsfall and his coworkers⁷ have reported that during convalescence they have obtained a positive agglutination test, using a specific strain of streptococcus isolated from a case of primary atypical pneumonia. None of these tests is specific, and while a positive finding with one of them may occasionally offer some confirmatory evidence in diagnosis, the particular interest in them seems to be in the clue that these findings may offer for discovering the causative agent of this pneumonia.

Before discussing treatment, I shall present a few case records in order to emphasize the clinical characteristics of primary atypical pneumonia. Chart I is of a patient having a moderate or mild course, the type of case that makes up almost 90 per cent of those seen. This girl, aged 20, was admitted to the Cornell University Infirmary on January

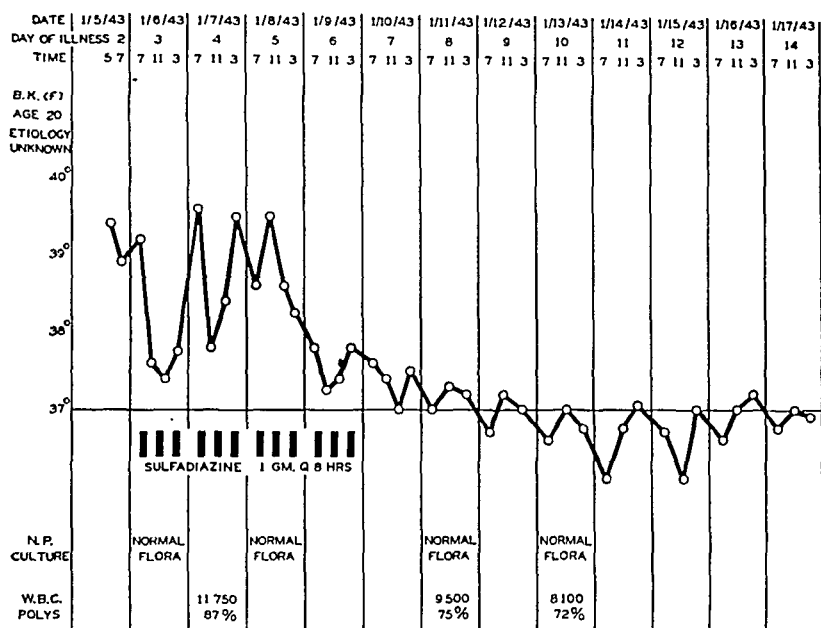


Chart. I. Mild case of primary atypical pneumonia, etiology unknown.

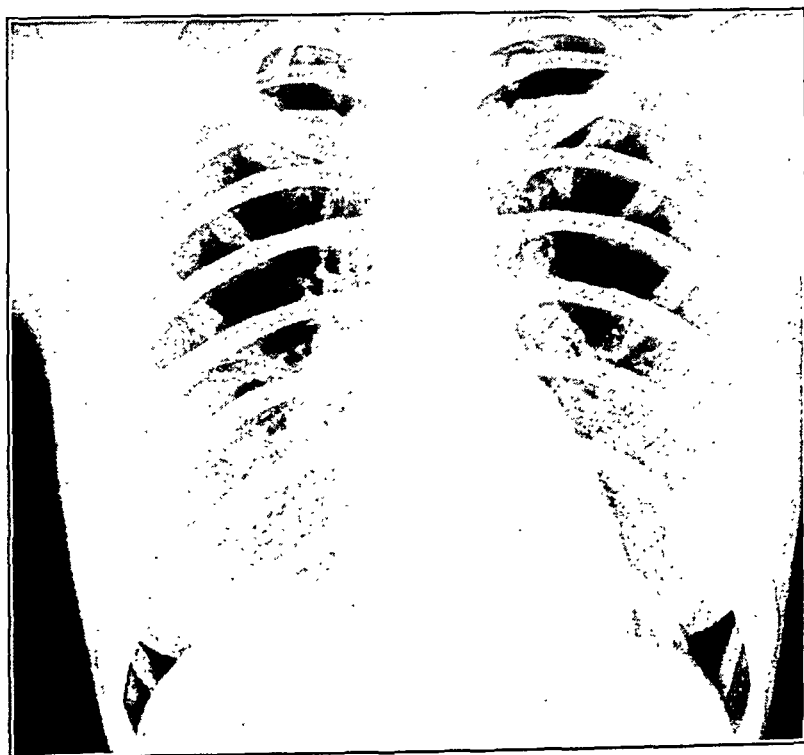


Figure 1. Chest x-ray taken on second day of illness in mild case of primary atypical pneumonia (Chart I). It shows a small area of light productive infiltration in the right base.

5, 1943. with a history of fever, chills, headache, and a general aching for one day. She had had symptoms of a "cold" for 2½ weeks. Physical examination revealed slight congestion of the upper respiratory tract and rales over the right lower lobe. The blood on January 7 contained 11,750 white cells, 87 per cent being polymorphonuclear cells. Chest x-ray (Fig. 1) was reported by Showacre of the Cornell Infirmary as showing a "small area of light productive infiltration in the right base." A diagnosis of primary atypical pneumonia was made.

The patient ran a moderately high intermittent fever for 4 days and then recovered by rather rapid lysis. She received sulfadiazine 1 Gm. t.i.d. for 4 days as part of an investigation, and it was believed not to have influenced the course of the infection. Nasopharyngeal cultures on January 6, 8, 11, and 13 showed only the usual flora. Special serologic studies for influenza virus identification were made by Thomas M. Magill but were negative.

With very few variations this case is being seen over and over again today. The diagnosis of primary atypical pneumonia is made by:

1. Gradual onset with chills, fever and cough.
2. Relatively high intermittent fever in a patient usually exhibiting very little cyanosis or dyspnea and no pleural pain.
3. A white blood cell count, usually within normal limits.
4. Positive chest x-ray.
5. Negative bacteriological studies.
6. No response to sulfonamides.

The next is a severe case of primary atypical pneumonia (Chart II). Fortunately for the doctor, only about 10 per cent are of this type, because they always present serious diagnostic and therapeutic problems. This patient was a girl, aged 19, admitted to Cornell University Infirmary on January 28, 1943, with a history of fever, chills, cough, headache, and pain behind the eyes for 2 days. Physical examination revealed slight congestion of the upper respiratory tract and slight dullness and rales over the left lower lobe. She appeared rather sick, had a flushed face, and a tight irritative cough. The white blood count was 13,500 with 88 per cent polymorphonuclear cells. On January 29, a chest roentgenogram showed a "slight irregular thickening of the pulmonary markings along the left heart border," and on January 30 there was a "definite area of linear infiltration in the left base along the left heart border." A diagnosis of primary atypical pneumonia was made.

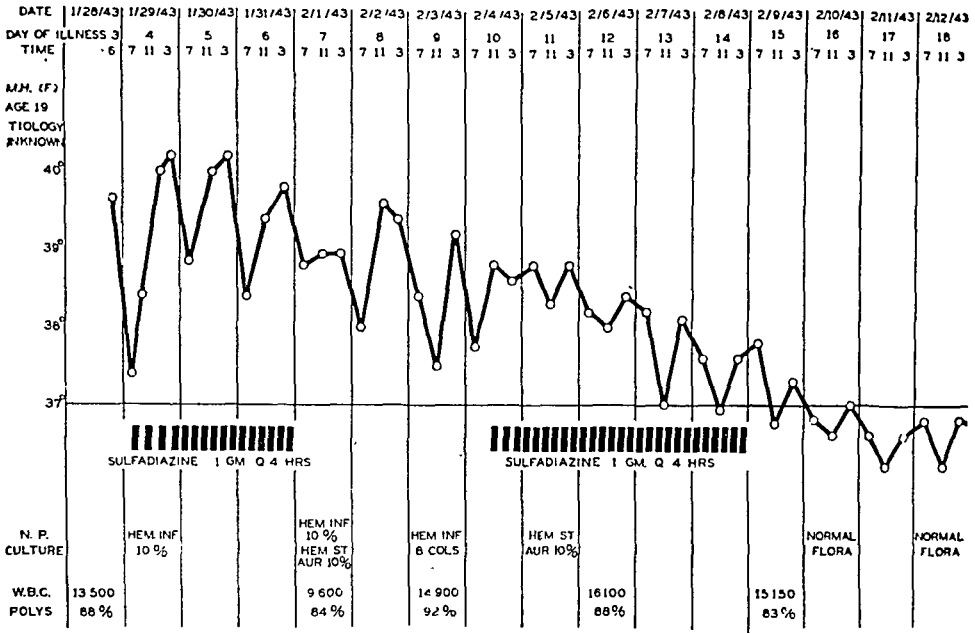


Chart II. Severe case of primary atypical pneumonia of unknown etiology.



Figure 2. Chest x-ray taken on tenth day of illness (Chart II) in a severe case of primary atypical pneumonia and showing extensive mottling throughout both lung fields.

Sulfadiazine 1.0 Gm. every four hours was commenced shortly after admission, chiefly because serious bacterial infection could not be ruled out. This was discontinued after 3 days because there was no response. On February 4 there were physical signs of spread into the right lung, the roentgenogram (Figure 2) showed "diffuse interstitial infiltration throughout the lower two-thirds of the left lung field and all of the right lung field except the apex, with scattered confluent 1-2 cm. areas in the outer third of the right lung," the white blood cell count was 14,900, and the nasopharyngeal culture showed *Hemophilus influenzae* and hemolytic *Staphylococcus aureus*. Because of these findings, sulfadiazine was started again and was continued for the ensuing five days, during which time the temperature dropped slowly to normal. Eventually recovery was complete clinically and by x-ray, although follow-up physical examinations revealed rales over the left lower lobe for two months.

In cases such as this one, the doctor will not be very secure as to the diagnosis or outcome until a specific diagnostic test is discovered. A high white count, which some authorities believe portends a more rapid recovery, and the finding of potential pathogens in the respiratory tract, which always suggests secondary invasion, confuse the picture of primary atypical pneumonia. We believe that response to the second course of sulfadiazine in this patient was more apparent than real. Response to sulfonamide therapy is more abrupt, as a rule.

The following case (Chart III) is that of an apparently genuine virus or psittacosis pneumonia. This patient, a 52-year-old woman, had had malaise, chills, fever, headache, and cough for 6 days before admission to Bellevue Hospital. On admission she was very much distressed by the cough and headache, but did not appear critically ill. There were many coarse rales and slight impairment of breath sounds over the right base. The sputum showed no significant organism. The leukocyte count was normal and remained so in spite of a high, irregular febrile course. There was no response to a 3-day course of sulfathiazole. Sulfadiazine given in the second week, however, may have exerted an influence on the infection. The x-ray (Figure 3) made on the 9th day of illness showed an extensive bronchopneumonia, much more pronounced on the right side. In this case there had been contact with pigeons, and six of eight birds examined had complement-fixing antibodies. The patient's serum in the second week showed a positive

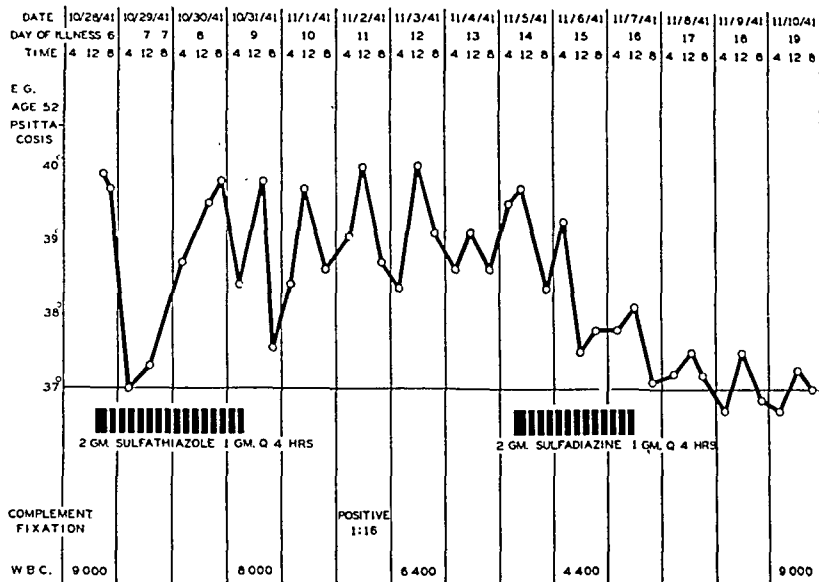


Chart III. Psittacosis pneumonia with severe course and recovery.



Figure 3. Chest x-ray made on ninth day of illness in a case of psittacosis pneumonia (Chart III).

complement fixation in a dilution of 1 to 16, and at a later time after full recovery, it was positive in a dilution 1 to 128. This apparently is a proven virus pneumonia, and its resemblance to the virus-type of the disease or primary atypical pneumonia is readily recognized.

The next case (Chart IV) shows a fatal psittacosis pneumonia in a 44-year-old woman, who was admitted after five days of illness and who died on the thirteenth day. No elevation of the white blood count was recorded until the day before death. The complement fixation test was positive in a dilution of 1 to 64 of serum. A virus identified as a member of the psittacosis group was isolated from the lung tissue.* The chest x-ray (Figure 4) taken shortly after admission to the hospital shows consolidation in the middle third of the right lung field. This x-ray film is not particularly different from that seen in pneumococcal pneumonia. Also it suggests cancer of the lung.

Finally we wish to present one case (Chart V) in contrast to those already included. This young man, aged 20, was admitted to the Cornell University Infirmary on January 4, 1943, with a history of a mild cold for about two weeks, followed by fever, headache, cough, and general aching for one day. He appeared acutely ill on admission and showed marked congestion of the upper respiratory tract, slight suppression of breath sounds and a few rales over the right lower lobe. The blood contained 24,000 white cells, 93 per cent polymorphonuclears. Chest x-ray (Figure 5) revealed a "small area of acute productive infiltration in the right cardiophrenic angle." The appearance of the x-ray in this case, the onset, and the fact that at the time there were thirty or more cases of primary atypical pneumonia in the Infirmary, all weighed strongly in favor of this latter diagnosis. However, an excellent rule to be remembered in such cases is: "When in doubt, use sulfonamide." Sulfadiazine was given 2.0 Gm. initially and then 1.0 Gm. q. 4 hours. After a high temperature spike to 41°C. a few hours after admission, there was a critical drop in temperature and rapid recovery. One of the two small post-critical rises in temperature may have been related to a remittance of sulfonamide therapy. Subsequent repeated nasopharyngeal cultures showed first a pure culture of pneumococcus Type 7, and then pneumococcus 7 and *Hemophilus influenzae*. The acuteness and severity of illness, the high white count on admission, and particularly

* The virus studies in the two psittacosis cases were carried out by Joseph E. Smadel and Louis Thomas of the Rockefeller Institute, and we are also indebted to Sarah Flanders of Bellevue Hospital for her efforts in completing the work-up of the Bellevue cases.

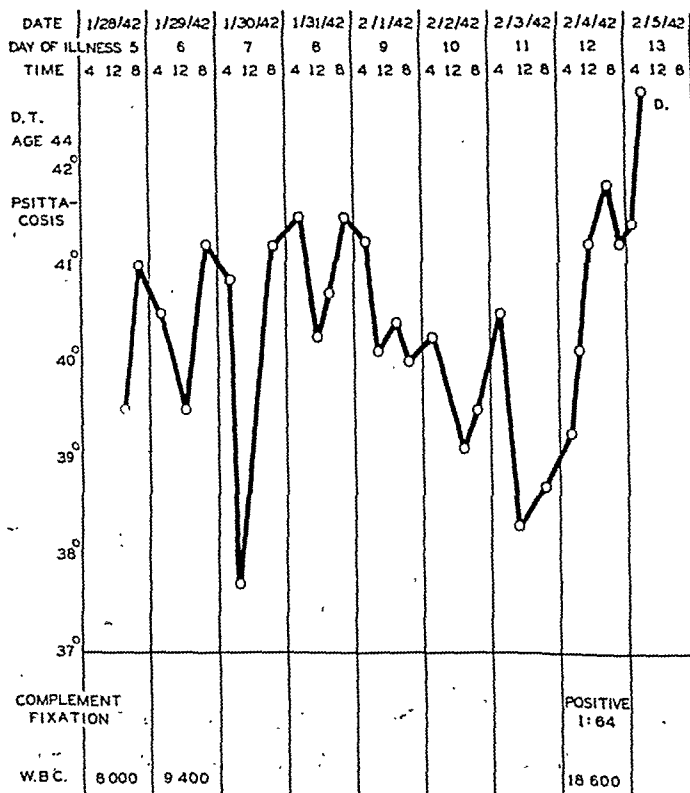


Chart IV. Fatal case of psittacosis pneumonia.

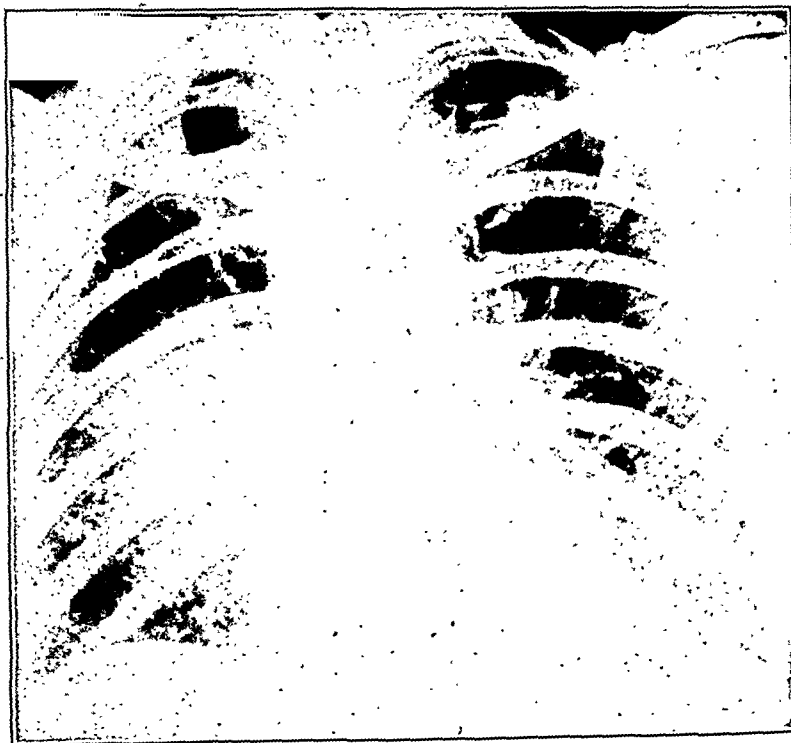


Figure 4. Chest x-ray on sixth day of illness in a fatal case of psittacosis pneumonia.

the rapid response to sulfadiazine are decided contrasts to the course and findings in the virus-type cases. Serious mismanagement occurs in these cases if sulfonamide therapy is withheld or delayed too long.

Primary atypical pneumonia enters the differential diagnosis of almost every respiratory infection. The milder cases commonly pass as influenza or "grippe" or "chest or grippy cold." The protracted cases must be distinguished from tuberculosis, bronchiectasis, and even carcinoma of the lung. The differentiation between primary atypical pneumonia and tuberculous pleurisy or any disease where there is a small pleural effusion can be very difficult. Recent reports that show bronchiectasis, pleural effusion and empyema as complications of primary atypical pneumonia must be evaluated very carefully, because in reality the suspected complications may represent the primary disease. A grave error is to mistake pulmonary infarct for primary atypical pneumonia, but the most serious mistake of all is to label a case of progressive pneumococcal infection as primary atypical pneumonia and to withhold specific therapy until it is too late to be effective.

The present treatment of primary atypical pneumonia is of about the same order as was the treatment of all pneumonia in the time of Sir William Osler. "It is a self-limited disease, which can neither be abated nor cut short by any known means at our command . . ." Furthermore, one should heed his counsel: "We should bear in mind that patients are more often damaged than helped by the promiscuous drugging which is only too prevalent."

We have already indicated in our discussion that the number one problem in treatment is *accurate and careful diagnosis*. Only a very few diagnostic procedures are necessary in the mild, transitory case (although we doubt that anyone can be accurate in diagnosing this disease without using the x-ray routinely). However, in the acute or severe case a large number of diagnostic procedures, particularly careful bacteriological studies, must be carried out and in a systematic way.

The second consideration is that of *wisely using or not using the sulfonamides*. Now it can be stated that primary atypical pneumonia per se is rarely ever benefited by the sulfonamides. Furthermore, proven secondary bacterial infection in this disease has been uncommon. The elevated white blood cell count late in the disease does not necessarily indicate secondary infection, but is probably a phase of the hemogram of this particular disease. In addition, finding a higher type pneumo-

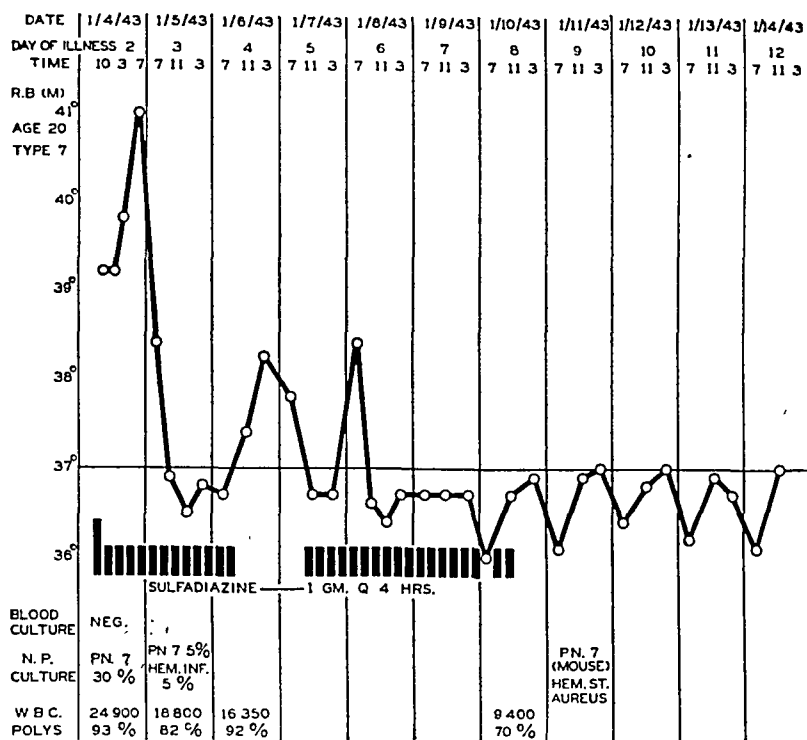


Chart V. Type 7 pneumococcal pneumonia.

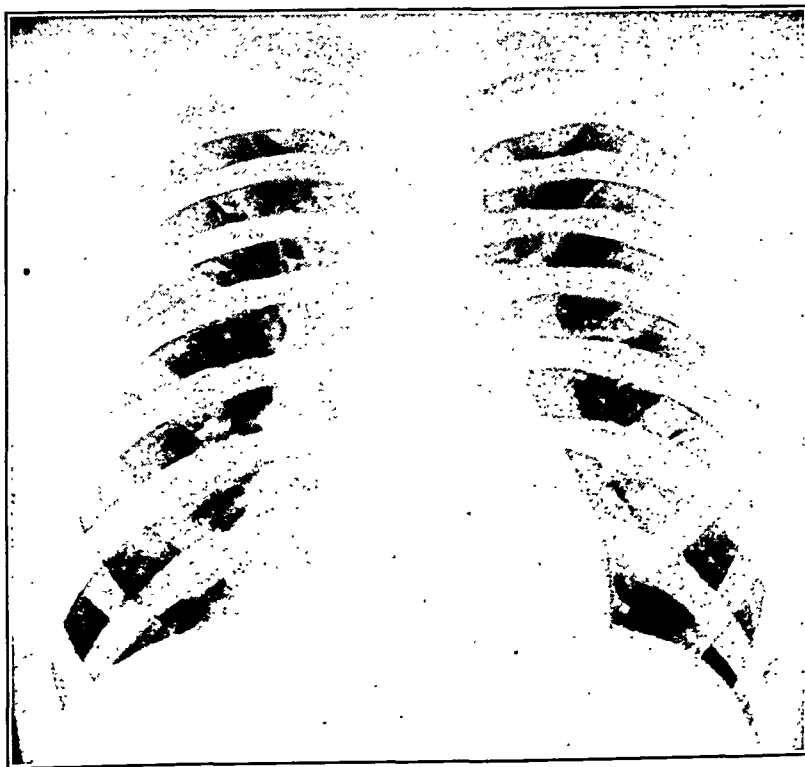


Figure 5. Chest x-ray in case of Type 7 pneumococcal pneumonia. Its appearance is very similar to that frequently seen in primary atypical pneumonia.

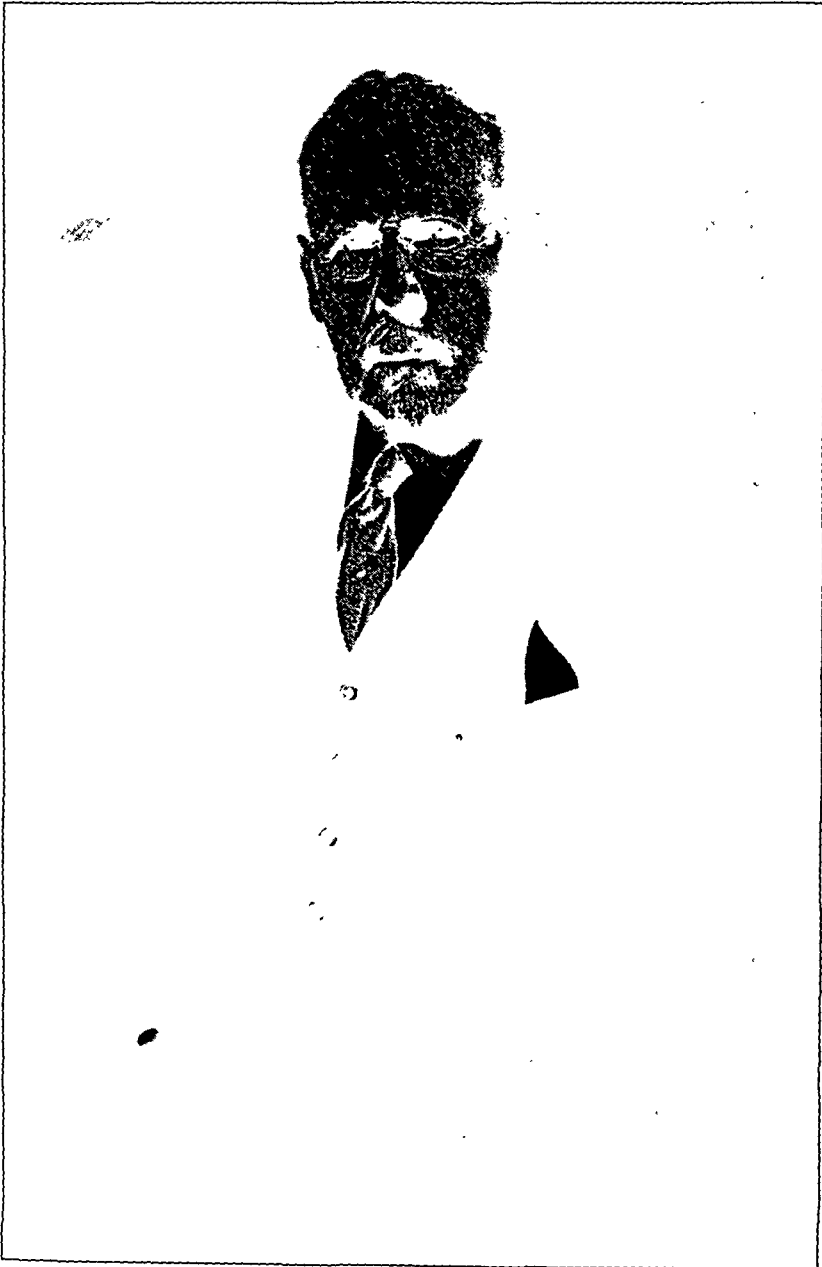
coccus or even a hemolytic streptococcus in the sputum does not mean that there is a secondary infection. What are the practical applications of this knowledge? We believe that on this basis the mild case is best treated *without* sulfonamide. However, the severe or doubtful one should receive a trial of the drug because of the danger of a mistaken diagnosis or a secondary infection, even though the latter has been rare. The trial should last not more than 3 or 4 days, during which time the dosage should be sufficient to insure a blood concentration of 5 to 10 mg. per cent. Sulfadiazine in our experience has proven to be the drug of choice, but should always be administered with sufficient alkali to keep the urine neutral or slightly alkaline. In a limited clinical trial, penicillin has been found to have no effect upon the course of atypical pneumonia.

The next consideration is a *judicious symptomatic and supportive therapy*. In this respect again we should divide the cases into the mild and severe. The mild one as a rule needs no treatment except rest and proper nursing care. The severe case, on the other hand, needs much attention and can tax every medical resource available. Oxygen, transfusions, and infusions occasionally are required. The cough, with chest soreness and general restlessness, is the most common symptom-complex. Here the physician can fully exercise the art of medicine and frequently he can control a serious situation by such simple measures and considerations as proper room ventilation, a chest binder, electric pad, oil of eucalyptus rubbed on the chest, or the use of a simple, non-irritating cough mixture. A few patients require sedatives, codeine, codeine and papaverin, or morphine; and when such treatment is indicated, it must not be postponed too long. The symptomatic treatment of severe cases of atypical pneumonia could be detailed at great length, but in the end it must be individualized both for the patient and the physician.

Finally, just as in the army with the soldier and the home folks, *the morale of the patient and his family is very important*. In a disease such as primary atypical pneumonia, which has a low fatality rate and rare complications but in which the course may be severe and protracted, the physician should be particularly generous with encouragement and explanation. This will be a most important part of the therapy of this disease until medical science evolves a specific etiology and therapy.

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BERNARD SACHS
1858-1944

IN MEMORIAM

BERNARD SACHS

W

E come here, all of us, with love and reverence to take leave and bid God-speed to a dear friend.

You have known him, so I can add little to what you know. You have been familiar, for perhaps scores of years, with his erect sturdy form, with his quick step, instinct with drive and purpose.

His light shone before men, and always to lead them and make easier their footsteps; and it shone the world over, wherever doctors met and talked together.

He radiated an old Roman Virtus—as I once said, one could not stand with him for ten minutes in shelter from a shower and not perceive in him an uncompromising honesty and a forceful goodness.

His rare hesitations in speech or action came only from his fear that he might wound in inadvertence. A gentleman is said to be one who never hurts anyone unintentionally, and Barney Sachs could and did fight doughtily for his idea of the right against wrong-thinking and wrong-doing, but never, in most of a life-time did I know of his being careless to a friend or colleague—indeed often he suffered some foolish ones overlong.

His friends knew his wisdom and his honour; many bequeathed to him burdens and great charges to be furthered when they themselves had left the scene of their endeavors, and we know the scruple and keen effort he used to make the aims of those good friends live on among men.

No honour was missing: to that within himself were added all those that could be given to one of our Profession; he was twice President of the American Neurological Association, President of the Academy of Medicine, and as President of the International Neurological Con-

gress, he made American Medicine refulgent in Europe. To all these, and to duties to his City, and to his pursuit of literature, he brought distinction of conduct and of word: but also, to each task he brought an immense energy which sprang, I know, from a great and unfailing love for his fellow man—a love which, with his skill, cured and assuaged the sick, and comforted the afflicted.

He loved, he toiled, he served, he *led*,
“Nothing is here for tears, nothing to wail
or knock the breast; no weakness, no contempt,
Dispraise or blame; nothing but well and fair,
And what may quiet us in a death so noble.”

FOSTER KENNEDY

RECENT ACCESSIONS TO THE LIBRARY

("Possession does not imply approval.")

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 3—*The New York Academy of Medicine Stated Meeting.* ¶ Executive Session. Reading of the Minutes. ¶ Papers of the Evening. Indications for and Value of Psychotherapy from the Practitioner's Standpoint. —a] The indications for psychoanalytic therapy, Franz G. Alexander, Professor of Psychiatry, University of Illinois, College of Medicine. b] Psychotherapy in general practice, S. Bernard Wortis, Lucius N. Littauer Professor of Psychiatry, New York University College of Medicine. ¶ Report on Election of Fellows.

FEBRUARY 17—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Fifth Harvey Lecture, "The Circulation in Traumatic Shock in Man," Dickinson W. Richards, Jr., Associate Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University.

SECTION MEETINGS

FEBRUARY 1—*Section of Dermatology and Syphilology.* ¶ Presentation of Cases— a] From The Mount Sinai Hospital. b] Miscellaneous Cases. ¶ General Discussion. ¶ Executive Session.

FEBRUARY 4—*Section of Surgery.* ¶ Reading of the Minutes. ¶ Presentation of Cases— a] Megacolon—bilateral lumbar sympathectomy—one year follow-up, Louis R. Kaufman, Metropolitan Hospital. b] Advanced hypertension—thoracolumbar sympathectomy—one and one-half year follow-up, J. William Hinton, Post-Graduate Hospital. c] Essential hypertension—Peet operation—eight and one-half year follow-up, Frederic W. Bancroft, Fifth Avenue Hospital. d] 1. Raynaud's disease of upper extremity—cervical sympathectomy—six

month follow-up. 2. Raynaud's disease of upper extremity—multiple anterior rhizotomies—two year follow-up. 3. Immersion foot—lumbar sympathectomy—eight month follow-up. 4. Hyperhidrosis—lumbar sympathectomy—two year follow-up, Bronson S. Ray, New York Hospital. ¶ Papers of the Evening—a] Physiology of the autonomic nervous system, Donal Sheehan, New York University College of Medicine (by invitation); b] The surgery of the sympathetic system, Captain James C. White, MC-V (S) USNR, Chelsea Naval Hospital, Boston (by invitation). ¶ General Discussion. ¶ Executive Session.

FEBRUARY 8—*Section of Neurology and Psychiatry and the New York Neurological Society.* ¶ Papers of the Evening— a] Disturbances in sleep mechanism, Charles Davison, Captain Edwin L. DeMuth (by invitation); Discussion, Samuel Brock, Henry A. Riley; b] Narcolepsy as a psychogenic symptom (case report), Leo A. Spiegel, C. Philip Oberndorf; Discussion, Samuel Brock, S. P. Goodhart; c] Sequelae and complications in shock therapy, S. Eugene Barrera (by invitation), B. L. Pacella (by invitation); Discussion, S. Bernard Wortis, Hubert S. Howe. ¶ General Discussion. ¶ Executive Session.

FEBRUARY 10—*Section of Pediatrics.* ¶ Reading of the Minutes. ¶ Presentation of Cases. ¶ Papers of the Evening. Pediatrics and the War—a] The Emergency Maternity and Infant Care Program—A federal plan for aiding Service Men's families, Leona Baumgartner; b] The effects of wartime conditions on infectious diseases of children, Ernest L. Stebbins; c] Juvenile delinquency and the war, Dudley D. Shoenfeld. ¶ General Discussion. ¶ Executive Session.

FEBRUARY 15—*Section of Medicine.* ¶ Reading of the Minutes. ¶ Papers of the Eve-

ning (*Fifteen minutes each*)—a] Cardiac manifestations due to allergy, Joseph Harkavy, Mt. Sinai Hospital; b] Clinical and chemical results of castration for metastatic prostate carcinoma, Alexander B. Gutman, Presbyterian Hospital; c] Vitamin studies in peripheral vascular failure, A. Wilbur Duryee, Ellen McDevitt, A.B. (by invitation), Bertrand Lowenstein (by invitation), Post-Graduate Hospital; d] Varices of the bronchial veins as a source of hemoptysis, John E. Deitrick, New York Hospital. ¶ Discussion led by William S. Tillett. ¶ Executive Session.

FEBRUARY 16—*Section of Genito-Urinary Surgery*. Order: ¶ Reading of the Minutes. ¶ Paper of the Evening—Operative indications in benign and malignant disease of the prostate (*slides and motion pictures*), Hugh H. Young, Johns Hopkins Hospital (by invitation). ¶ General Discussion—George F. Cahill, Roy B. Henline, Joseph F. McCarthy, Alexander R. Stevens. ¶ Executive Session.

FEBRUARY 16—*Section of Otolaryngology*. ¶ Reading of the Minutes. ¶ Presentation of a New Instrument—Pharyngological Photoelectric Colorimeter, Samuel J. Kopetzky. ¶ Papers of the Evening—a] Congenital laryngeal stridor (Inspiratory laryngeal collapse) (*motion pictures*), Leo Schwartz; b] Radiation and surgery in the treatment of tumors of the hard palate and nasal sinuses, G. Allen Robinson. Discussion, Andrew A. Eggston, John M. Lore; c] Treatment of certain forms of deafness, tinnitus and dizziness by means of benzyl cinnamate. (Cases presented), Jacob Jacobson (by invitation). Discussion, Samuel J. Kopetzky.

FEBRUARY 18—*Section of Orthopedic Surgery*. ¶ Reading of the Minutes. ¶ Presentation of Cases—a] Osteoid—osteoma of the lumbar spine *From the Hospital for Joint Diseases*, Francis B. Roth

(by invitation); b] Scoliosis in twins, Frederick Vom Saal (by invitation). ¶ Papers of the Evening—a] Plantar flexed talus, Frederick R. Thompson. Discussion opened by Alan DeForest Smith; b] Hemifusion in tuberculous joints, John R. Cobb. Discussion opened by David M. Bosworth. ¶ Executive Session.

FEBRUARY 21—*Section of Ophthalmology*. ¶ Instruction Hour. Diagnosis of the heterophorias, James W. White. ¶ Reading of the Minutes. ¶ Case Reports—a] A further report on a case of lateral proboscis with cyclopean eye, Louise H. Meeker, Rudolph Aebli; b] Intrinsic variability of astigmatic errors, Joseph I. Pascal (by invitation). ¶ Papers of the Evening—a] Differential diagnosis of paresis of the obliques and superior or inferior rectus (*moving pictures*), W. Thornwall Davis, Washington, D. C. (by invitation). Discussion, James W. Smith; b] Effects on high altitude flying and deep sea diving on ocular function, Commander Leon D. Carson, M.C. USN (by invitation). ¶ Discussion, Conrad Berens.

FEBRUARY 29—*Section of Obstetrics and Gynecology*. ¶ Executive Session, Reading of minutes. ¶ Case Report—Artificial insemination from donor. Clinical study of six successful cases and three failures. (*lantern slides*), Marie P. Warner (by invitation). ¶ Paper of the Evening. Treatment of uterine prolapse. (*Lantern slides*), H. W. Johnson (by invitation). ¶ General Discussion.

AFFILIATED SOCIETIES

FEBRUARY 16—*New York Section Society for Experimental Biology and Medicine in affiliation with The New York Academy of Medicine*. ¶ Papers of the Evening—a] Phosphorus metabolism in gravity-shocked rabbits, W. L. Nastuk (by invitation), (introduced by W. H. Cole); b] Two fractions of substances

in shed blood which contract smooth muscle, M. B. Zuker (by invitation), J. J. McBride (by invitation), C. Tsai (by invitation), (introduced by M. I. Gregersen); c] The determination of biological values of proteins, J. B. Allison (by invitation), J. A. Anderson (by invitation), R. D. Seeley (by invitation), (introduced by W. H. Cole); d] Remarks on the structure and properties of the thromboplastic protein, E. Chargaff, A. Benedich (by invitation), S. S. Cohen (by invitation), D. H. Moore (by invitation); e] The discrete extensor plantar response, a sign of extrapyramidal damage, F. A. Mettler; f] Arrest of endocarditis due to *Streptococcus viridans*, W. J. MacNeal, A. Blevins (by invitation), A. E. Slavkin (by invitation), C. A. Poindexter (by invitation); g] Combined penicillin and heparin treatment of subacute bacterial endocarditis; experimental and clinical study, L. Loewe (by invitation), R. Rosenblatt (by invitation), H. Greene (by invitation), M. Russell (by invitation), (introduced by W. J. MacNeal).

FEBRUARY 21—*The New York Roentgen Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the Evening—a] Cartilaginous injuries of the knee joint as incurred in the Navy, Lt. Comdr. Marvin A. Stevens, M.C., USNR (by invitation). Discussion, Philip D. Wilson (by invitation); b] Some notes on the roentgen examination of the injured knee, Lt. Comdr. Jacob Gershon-Cohen, M.C., USNR (by invitation). Discussion, Raymond W. Lewis. ¶ General Discussion. ¶ Executive Session.

FEBRUARY 24—*The New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Presentation of Cases. Histology of the lymphoid tissues in measles, Vera Dolgopol. ¶ Papers of the Evening—a] Experimental argyrosis, Charles T. Olcott; b] A comparative survey of diagnostic serologic findings in relation to syphilis, Howard Fox (by invitation), John F. Mahoney (by invitation). ¶ Executive Session.

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
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JUNE 1944

THE INDICATIONS FOR
PSYCHOANALYTIC THERAPY*

FRANZ G. ALEXANDER

Director of Institute for Psychoanalysis, Chicago
Associate Professor of Psychiatry, University of Illinois, College of Medicine, Chicago

A FEW years ago it would have been much easier for me to speak about the indications of psychoanalytic therapy. In the last five years one of my main interests has been to inquire into the possibility of applying the dynamic principles of psychoanalysis to therapy in a more flexible manner than is customary in the standard psychoanalytic procedure. In the Chicago Psychoanalytic Institute our Staff has attacked this problem by trying to adapt the psychoanalytic technique to the different types of patients. As long as the psychoanalytic procedure is considered as a standard procedure the question of indications is a relatively simple one. The problem is, then, to select those patients who fit the technique. In the field of therapy such a state of affairs is not a satisfactory one. There are very few examples in medicine in which the therapeutic tool is fixed rigidly and the patients are selected to fit the tool. The logic of the therapeutic situation requires the opposite approach. The patients' ailments are different, and the patients them-

* Read at the Stated Meeting of The New York Academy of Medicine, February 3, 1944.

selves, their constitution, physical and psychological make-up vary considerably; the physician's task is, after making a diagnosis, to choose a therapy which is suitable for the specific case. In our field for a long period, in fact, until very recently, the situation was the opposite. There was a highly refined instrument, the psychoanalytic therapy, a highly standardized method which the psychoanalyst had learned to handle in a three to four years' curriculum after his graduation and one year psychiatric internship. Most psychiatrists, after learning this method, specialized themselves in the exclusive use of this one standard technique. If he was a man of sound judgment the psychoanalytic practitioner carefully selected those patients who were suitable for the technique which he had learned to handle. Only a minority tried to adapt the procedure according to the different types of cases. Those patients who did not need this prolonged and intensive form of psychotherapy, as well as those who were, in a sense, too sick to be treated this way, were usually referred to other colleagues. The nature of psychoanalytic practice favored this attitude. According to the standard technique patients are seen five to six times a week for a 50 to 60 minutes' interview. After a psychoanalytic practitioner has filled his time with seven to nine daily patients he is scarcely in a position to treat patients with techniques which require other time arrangements. If he has a free hour he will be inclined to fill it with another patient who requires the same kind of approach. Therefore, a great number of psychoanalysts of the old school had little opportunity or inclination to utilize their theoretical knowledge of psychodynamics for experimenting with other technical procedures.

As is well known, the expression psychoanalysis applies to three different things: (1) it is a psychodynamic theory of personality and its disturbances, (2) a method of investigation, and (3) a therapeutic procedure. For a number of reasons the therapeutic procedure and the method of investigation have remained practically identical for a long period. In the past this coincidence of the method of therapy with that of research had valid reasons. The essence of psychoanalytic therapy is to bring into the patient's consciousness, emotions and motivations of which he is not aware, or in other words, to extend the patient's conscious control over his behavior. This requires a thorough knowledge of the patient's personality structure, both on the part of the therapist and the patient. In this sense the patient's therapeutic needs

coincide with the analyst's investigative aim. This explains why for such a long time psychoanalytic therapy and psychoanalytic research could be carried out by the same method, the analytic treatment of patients.

No etiologically oriented therapy can be developed without a thorough knowledge of the causes and nature of the disease. Freud attacked a practically unknown territory. In order to develop a sound therapeutic procedure which is not based on mere empiricism he had to explore the nature of neurotic disturbances and that required a knowledge of the dynamic structure of the total personality. The fact that he could utilize for therapeutic purposes a method which at the same time was a method of investigation accounts for the fact that psychoanalytic therapy and theory have developed hand in hand and that an originally modest therapeutic aim has led to the foundations of a new discipline, a dynamic theory of personality. The price for this great initial advantage we had to pay much later. Freud's main interest was, of necessity, investigative. We inherited his highly developed and standardized technique in the shaping of which his investigative interest played such an important role and continued to utilize it in the same manner for almost 40 years. We must admit that our field has lacked flexibility in therapeutic orientation. As long as one knew so little about the pathogenesis and pathology of neurotic disturbances it was justifiable, desirable, and unavoidable to study each case in extenso: each patient was at the same time a subject of research. With the advancement of our knowledge the time has now come when we can utilize sound generalizations and well established principles for a more direct and economic therapeutic procedure.

Since I have been using the principles of psychoanalysis more flexibly in my treatments, I can no longer answer the question, "In which cases is psychoanalysis indicated?," without certain qualifications. Today this question sounds to me almost like asking, "In which case is surgery indicated?" Obviously the answer is not very satisfactory without telling which type of surgery. The removal of a foreign body, the cleaning, dressing and suture of a superficial wound, and laparotomy, are all surgical procedures based on the knowledge of anatomy, physiology and bacteriology. I believe we are now entering a similar stage in psychiatry. We can no longer consider the psychoanalytic technique as something fundamentally different from other psychotherapeutic

procedures that are based on the dynamic knowledge of the human personality.

To state all this more concretely, let us compare two types of cases. The first is a fairly well-adjusted soldier in his 20's, who has never manifested before any chronic personality disorder, and who, after having been exposed to extreme strains in combatant service, develops a traumatic neurosis manifesting itself primarily by psychosomatic symptoms. This soldier will obviously require a radically different therapy from that suitable for a man of the same age who was a problem child, and in early adolescence had developed obsessional and compulsive symptoms, and who was unable to complete his university studies because of his incapacitating obsessional states which were combined with rituals consuming the major part of his day. The common feature of the psychotherapeutic approach to these two cases will be only that the procedure must be based on the psychodynamic knowledge of the disturbance. Moreover, the psychotherapist will have to understand not only the nature of the case but also the dangers which his therapeutic procedure entails. He must be well acquainted with the theory of transference and resistance and also with the pathogenesis and pathology of emotional disturbances. Then it is a secondary consideration whether he should see the patient six times a week for an hour, having him on the couch and using the method of free association, or see him three or four times all together, or treat him once or twice weekly in face to face interviews. In the Chicago Psychoanalytic Institute, for example, we may see the patient for awhile in daily interviews using the method of free association and later switch to less frequent interviews, exchanging the couch with the chair. In other cases the opposite sequence might be indicated. We may begin by seeing the patient in infrequent interviews, changing gradually to the method of free association on the couch in more frequent interviews.

You will now appreciate my previous statement concerning the difficulties of discussing the indications for psychoanalytic therapy in a restricted sense. In order to answer this question one must at first clearly define what is psychoanalytic therapy. The answer will depend upon the nature of the definition; whether one defines psychoanalysis by such external criteria as the frequency of interviews, the utilization of the couch, and the method of free association, or one defines it by more essential criteria: as a therapy which utilizes the phenomena of

transference and resistance to increase the patient's ability to find ego-syntonic gratification for his subjective needs.

I have come to the conclusion that this therapeutic aim can be achieved by the use of different therapeutic techniques. In psychoanalysis it is customary to distinguish three therapeutic factors: abreaction, insight, and working through. By abreaction is meant a discharge of repressed emotions. This becomes possible in the permissive atmosphere of the psychoanalytic sessions, the therapist's attitude being only understanding and not judging. Mobilization of repressed emotions in itself, without insight, however, has only a limited temporary therapeutic value. On the other hand the emotional discharge, if it does not exceed a certain intensity, makes insight possible, since the freely expressed emotions are now exposed to the integrative faculties of the conscious mind. Too intensive emotions are not favorable, for intellectual grasp is impossible when emotions run wild. The right combination of emotional experience and insight is the essence of psychoanalytic therapy. Working through refers to the deepening of this insight by bringing the uncovered material in connection with the rest of the conscious mental content, with the patient's past and present experiences. It is then a secondary question which technical devices should be utilized to bring about emotional discharge, insight, and a thorough digestion of the uncovered unconscious material. Whether the emotional discharge takes place on the couch while using the method of free association or in a directed conversation between patient and therapist sitting face to face, or whether it takes place outside of the analytical interviews in actual life situations while the patient is under the influence of the psychoanalytical interviews, all these are technical details to be decided according to the individual nature of the case. In certain cases it is imperative that the emotional discharge and insight take place very gradually, in small quantities in daily interviews; with other patients whose integrative power is greater, emotionally highly-charged but infrequent interviews are possible or even preferable. All this depends upon the patient and the phase of the therapeutic procedure.

It is important to recognize that not even the standard psychoanalytic therapy consists merely in free associations and interpretations. The course of associations is occasionally interrupted by directed conversation and the emotional discharge takes place not only on the couch

but also at home, in the country club, and in the office. Furthermore, the integrative process is by no means the sole accomplishment of the psychoanalytic interpretations, just as little as the growing together of the two surfaces of a surgical incision is the accomplishment of the surgeon. The ego's natural function is that of integration and the psychoanalyst merely supports this natural synthetic function of the ego. As the surgeon's function is to create the best conditions for the wound to heal, so does the psychoanalyst by proper management of the transference and resistance create the most favorable conditions for the native integrative functions of the ego.

Modern psychoanalytic therapy as we use it in the Chicago Psychoanalytic Institute has added to the inventory of the well-known technical devices, the manipulation of the frequency of interviews, changing from the face to face interview to the couch and vice versa, interruptions of longer or shorter duration and the combination of psychotherapy with drug and dietary treatment. The technical devices will probably still increase; the fundamental principle, however, remains the same: To create conditions which favor the ego's synthetic powers.

The question for indication can be only answered adequately from this perspective. When a patient consults us we do not accept him for any specific method of psychotherapy, whether it be daily interviews on the couch for a year or weekly consultations over a definite period of time, or only two or three interviews all together. The choice of the specific procedure will be based upon diagnostic opinion and not even after the initial diagnostic appraisal can we decide in advance what technique will be used in a later phase of the treatment. As I now practice psychoanalysis it is exceptional that I use the one and the same technique from the first to the last day of the therapy. I have completely discarded the idea that psychoanalytic therapy consists rigidly in daily interviews on the couch and in using the method of free association all the time. If that is what is meant by psychoanalysis I cannot answer the question of indication at all because at the beginning of a treatment and even for some time after I have undertaken the treatment of a patient I do not yet know how nor when I may change my technique. Much depends upon the patient's progress and occurrences during the treatment, which cannot be predicted.

Every form of psychotherapy must be based on a sound knowledge of psychodynamic principles. With this qualification in mind one can

well distinguish two types of psychotherapy, one primarily supportive therapy and one aiming at insight; that is to say, an uncovering type of psychotherapy. In cases in which the ideal aim of psychotherapy, namely, to extend the synthetic functions of the ego over repressed impulses, must be abandoned on account of a constitutional or acquired weakness of the ego, supportive therapy is indicated. This consists mainly of aiding the ego's spontaneous defense mechanisms and in satisfying the patient's need for assistance by actual guidance. Inferiority feelings are not traced back to their origin but are combated with reassurance; anxiety is relieved through assuming a protective role; guilt feelings are not explained but relieved by permissive attitudes. The effect of such a supportive approach is limited and it requires a continuous, although not necessarily frequent, contact with the patient; in a sense it is interminable. Apart from the patients with an underdeveloped ego there is another group on the opposite end of the scale which also can be helped by merely supportive measures. I mean previously well-adjusted patients who are suffering from an acute neurotic disturbance which developed under the pressure of unusually difficult external conditions.

Under the weight of evidence offered by the facts of experimental neurosis of animals, and even more by the experiences of war psychiatry, we will have to discard the traditional view that a neurosis is a condition which etiologically always goes back, if not to constitution, at least to infantile experiences. Instead we will have to accept a more relativistic concept of neurosis. Psychoneurosis consists in a failure of the ego to deal with a given situation, that is to say, in a failure of its basic function to find gratification for subjective needs under the given circumstances. In chronic cases the functional capacity of the ego may be impaired constitutionally or as a result of traumatic experiences of childhood. In acute cases a well functioning ego may break down under extraordinary difficulties with which to cope is beyond the person's ability. In any case the failure of the ego is dependent upon the relation of its functional capacity to the difficulty of the problem which it has to face. Accordingly, every person may potentially develop an acute neurotic state when exposed to difficulties beyond his powers of adaptation. There are numerous acute neurotic states occurring in persons with an ego which in the past always functioned well and performed

its tasks successfully.* However, under the pressure of unusual traumatic conditions which appear either utterly hopeless or create acute anxiety, the ego's synthetic capacity diminishes. In these cases the patient's confidence in the therapist, the emotional support which he receives from the interviews, may reduce the anxiety or hopelessness and restore the ego's efficiency which was temporarily reduced under the influence of paralyzing emotions.

The treatment of many acute cases of war neurosis may well illustrate this point. In such cases there is often no need for extensive interpretative work. The reassuring contact with the physician may restore the ego's functions which were impaired temporarily under the influence of anxiety or discouragement. In contrast to such supportive measures we may define psychoanalytic therapy as all the uncovering types of procedure which aim at inviting unconscious material into consciousness and then helping the patient through interpretative work to bring these newly won psychodynamic quantities into harmony with the rest of his personality. As has been stated before, this therapeutic aim can be achieved by different techniques which, however, always consist in a right combination of emotional discharge, insight, and integration. The standard psychoanalytic technique is only one of the various uncovering procedures. It must be emphasized, however, that it contains all the therapeutic factors known at present and other uncovering techniques differ from it only in quantitative aspects such as the frequency of interviews, interruptions, and the extent to which

* Freud, in his original etiological formulation, expressed the same view. According to this formulation in the causation of neurosis, constitution and infantile experiences on the one hand and traumatic experiences of later life (frustrations) on the other stand in a complementary relationship to each other. "For the consideration of the causes of neuroses, we may arrange neurotic diseases in a series, in which two factors, sexual constitution and experience, or, if you wish, libido-fixation and self-denial, are represented in such a way that one increases as the other decreases. At one end of the series are the extreme cases, of which you can say with full conviction: These persons would have become ill because of the peculiar development of their libido, no matter what they might have experienced, no matter how gently life might have treated them. At the other end are cases which would call forth the reversed judgment, that the patients would undoubtedly have escaped illness if life had not thrust certain conditions upon them. But in the intermediate cases of the series, predisposing sexual constitution and subversive demands of life combine." . . . "Within this series I may grant a certain preponderance to the weight carried by the predisposing factors, but this admission, too, depends upon the boundaries within which you wish to delimit nervousness." ("A General Introduction to Psychoanalysis," Prof. Sigmund Freud, LL.D.; New York: Boni & Liveright, Inc., 1920; p. 301). Since psychoanalysis mainly dealt with chronic cases the significance of this formulation has been gradually forgotten and the universality of infantile neurosis as the etiologically important factor in every neurosis has been postulated. This is, however, obviously contrary to Freud's original formulations, which recently in cases of acute war neurosis found an impressive verification. (See also pp. 314-315, loc. cit.).

free association or directed interviews are used. If we want to reserve the expression psychoanalysis for the standard technique, we may call these briefer techniques analytically oriented psychotherapy. I would, however, be inclined to extend the definition of psychoanalysis to all uncovering procedures which are based on the combination of emotional discharge, insight, and integration of the newly uncovered material. It does not seem advisable to classify psychotherapeutic techniques according to such details as the frequency of the interviews, and the duration of the treatment. The important criteria are the psychological processes on which the therapy is based.

In all those cases in which we have reason to believe that the patient's ego will not be able to withstand the uncovering type of approach, all forms of uncovering technique are contraindicated. In other cases a combination of uncovering and supportive techniques may be applied. The decision concerning frequency of interviews and other technical details can be best made during the treatment. In general, in chronic cases more frequent interviews are indicated and it is advisable to count on a long analysis. The frequency of the interviews and interruptions, however, do not depend entirely upon the severity of the case. A strong, dependent type of transference often can be made fully conscious only by reducing the frequency of the interviews or even by the help of shorter or longer interruptions. A radical reduction of the frequency of interviews is often indicated in that typical phase of an analysis in which the emotional gratification derived from the interviews begins to outweigh the patient's desire for recovery. In the majority of analyses such a phase occurs sooner or later.

For the choice of a suitable technique the estimation of the functional efficiency of the ego is of paramount importance. An indispensable guide in forming such an opinion is the study of the patient's life history; that is to say, a review of past performances. However, the presence or absence of neurotic states in the history in itself does not reliably indicate the ego's functional efficiency. Following the relativistic concept of neurosis it is important to consider the external difficulties under which the past neurotic failures took place. As has been stressed before, under extreme difficulties even a well functioning ego may crack. Consequently, a history of repeated or chronic neurotic conditions under relatively favorable external circumstances is indicative of a severe ego disturbance; the same type of neurotic states, if

provoked by extremely traumatic conditions, may not be the signs of a very weak ego.

Apart from a careful evaluation of the past history, the Rorschach test is claimed to give valuable leads for the estimation of the ego's integrative capacity. I do not feel competent to discuss the validity of this claim.

A third and particularly helpful method consists in giving careful trial interpretations as early as possible. The patient's reaction to such initial interpretations is the best guide in evaluating the patient's capacity for insight as well as the character and the extent of his resistance and future coöperation. Let me illustrate this method by an example.

A business man nearly 60 years old consulted me on account of a street phobia which prevented him from going to his office down town. He came with his wife, who stayed in the waiting room during the consultation. He lived in a suburb and had no difficulty in walking in his garden or nearby streets, but he dared to go down town only when accompanied by his wife. At the beginning of his illness he occasionally went to his office but gradually stopped going and would not leave his garden. He had two younger partners with whom he had an agreement that his income would not change even though he no longer actively participated in the management of the business.

In the first interview, which turned out to be the last one, he explained to me that his street phobia followed as the aftermath of an acute condition which he called a sun stroke. Apparently he took a sun bath in his garden and developed an acute dermatitis which lasted for a few days. He expressed great concern over the fact that on account of his present condition he was compelled to neglect his business. When I asked him about the details of his contract, after some hedging he told me that his income was secured independently of his activities in the office. Then I expressed my admiration for such an advantageous arrangement but he did not share in the least my admiration and stressed the fact that he had no great confidence in his younger partners' ability to carry on the business successfully without his help. I asked him to tell me in detail his reasons for not trusting his partners' ability. He became very defensive and involved himself in all kinds of contradictions. As the consultation went on it became more and more obvious that in the last few years the ageing patient was no longer able to participate as intensively as before in the company's

affairs. Apparently in former years he had been a capable executive but now he could no longer keep pace with his younger partners. It was not difficult to reconstruct the actual situation among the three partners. The two younger ones tried tactfully to make the patient understand that the interest of all of them would be best served if the patient retired and that they did not mind in the least if he continued to draw the same income as before. All this transpired clearly from our conversation although the patient himself did not realize the situation. He was completely unable to accept the unalterable fact that his mental and physical powers were steadily declining and he was no longer able to contribute as much as his younger partners. The phobia which he could explain on a physical basis as the result of a sun stroke and as a passing condition gave him an escape from admitting to himself his progressive decline. His was by no means a senile or even pre-senile condition. But his relation to his younger partners radically changed; he was no longer their leader, not even their equal. He persuaded himself that he was staying away from business not because he was unable to face his changed status in relation to his partners but because of a temporary sickness. Actually he was now dependent upon his two partners; he displaced this actual dependence with a neurotic dependence upon his wife. He regressed to the infantile form of helplessness, to that old insecurity which he experienced when he first had to walk alone on the street. Of course the meaning of this regression as a return to infantile insecurity was unknown to him and therefore, the phobia could save him facing his actual dependence and the unalterable fact of ageing with all the conflicts connected with it. Obviously this neurosis was a good bargain. He exchanged a greater evil for a lesser one. It was easier for him to suffer from a phobia than to admit that he must cede his place to the youth. After having understood this emotional situation I hardly could hope to cure his condition. What compensation could I have offered him for depriving him of the alibi of sickness? Financially he was secure and going to his office was for him merely a question of prestige. Giving up his phobia would have necessitated admitting the fact that he was becoming more and more incompetent. Accepting ageing is, of course, a universal problem of everyone but in his case this universal problem was aggravated by a number of circumstances. He had to admit not only his decline but on account of his contract also that he had become a parasite; that he, the former

leader, had become a nuisance in the office. The street phobia resolved all these problems. He was sick and therefore entitled to have his revenue without losing face.

There were still other factors which contributed to his emotional impasse. A person who, during his past life, has learned the art of leisure and has developed creative interests which do not require the same intensive activity as business, or who has learned in the past to enjoy contemplation, will accept old age easier than a man of action who spent his life exclusively in a race for prestige. What I learned about the patient's past did not offer much hope in these respects. He was a self made man with limited interests who had fought his way from poverty to financial success. His self esteem was based exclusively on his accomplishments as a business man.

Unquestionably we deal here with imponderables. We do not have a scale in psychiatry, hence the precise evaluation of quantitative factors is not possible. However, trial interpretations may give us an approximate idea about the intensity of the resistance and allow a more realistic estimation of the therapeutic chances. I cautiously began to explain to the patient that his phobia had an emotional and not a physical origin. I immediately met with a massive resistance. He was convinced that the whole condition was a result of his sun stroke. Here I did not get even to the first base so I let up another "trial balloon." I proceeded to intimate tactfully that he might misjudge his partners' ability to conduct the business without his help. He was adamant in his opinion. Then I began to approach him from another angle and discuss with him the emotional difficulties of retirement in general. I said to him that often a person does not want to realize that he has outgrown his usefulness. The patient became markedly restless. I continued to tell him how difficult it is to cede one's place to the youth. I added that I was somewhat doubtful concerning the validity of his criticism of his partners. I called his attention to the fact that his statements concerning them were quite contradictory. The more I tried the clearer it became that no matter how tactfully I proceeded it would be impossible to make him see the unpleasant truth. Why should he not retire believing that he is indispensable instead of realizing that his partners considered him a nuisance? Oscar Wilde said once: "If you tell the truth eventually you will be found out." I preferred to be found out right away and I told him the truth as tactfully as possible;

namely, that he could not face the change in his life situation, the fact that formerly he was the leader of his younger partners and now they wanted to get rid of him. I emphasized the universality of this experience and ended by saying that he had done his share in life and why could he not now retire and enjoy his old age in quiet? When I was through with my appeal the patient jumped up from the chair and in a shrill voice called out to his wife in the waiting room, "Mama, let us go home!" The wife came in, took the old gentleman by his hand and they departed.

I never heard from him again but his wife telephoned me a few days later that her husband did not mention any more going down to the office. I think I saved the patient a long analysis and myself a therapeutic failure. Would the patient have shown a somewhat less massive resistance after my first interpretation I would have changed my whole strategy.

In the case of a 66 year old business man who developed chronic alcoholism and spastic colitis after his retirement, my initial trial interpretations concerning similar emotional difficulties of retirement, involving hurt prestige, and envy of the youth, were met with considerable understanding and did not in the least deter the patient from continuing the treatment. I saw him at first twice, later once every week. After thirty interviews the treatment was successfully terminated.

There were various factors which made this patient more accessible for therapy. He was not exposed to such an humiliating change in his role as a business man as the first patient, his retirement did not hurt his pride to the same extent because his prestige was not as closely connected with his position and had a broader basis. Furthermore, his wife had a fine understanding for his emotional problems and had a less conventional outlook than the patient himself. This was a great help in the therapeutic task to bring about a reorientation and changing the patient's previous prestige values. All these factors, of course, could not be appraised in the initial interviews. However, the fact alone that this patient did not shy away from the first trial interpretations but without accepting them right away was at least capable of considering them with an open mind and a constructive curiosity was a reliable indicator of a good therapeutic chance.

In dealing with the problem of indication it is important to bear in mind that when significant internal and external factors are un-

changeable the best solution in some cases may be a neurosis. The patient's reactions to initial trial interpretations are often helpful in discovering these cases right at the very beginning.

SUMMARY

Every psychotherapy should be based on sound psychodynamic principles and the understanding of the specific structure of each individual case. One can differentiate between two types of psychotherapy, supportive and uncovering therapy. All uncovering therapeutic procedures are based on the same principles as the standard psychoanalytic technique; on the right combination of emotional discharge, insight, and integration of the uncovered material. The variations are of a quantitative nature concerning frequency and the number of interviews, interruptions and the extent to which free association, or more directed interviews are used. The variations of the technique are applied according to the psychodynamic situations as they evolve in the course of the treatment. The criteria for the initial choice of technique are derived from observations revealing the degree of the ego's functional efficiency. Among these observations the most important ones are supplied by the past performances of the ego as revealed in the life history. The patient's reactions to initial trial interpretations are of great value in the evaluation of the intensity of the patient's resistance, his future coöperation, and of the chances of the treatment.

SOME PSYCHOSOMATIC AND THERAPEUTIC ASPECTS OF WAR NEUROSES*

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IT is obvious, as we study a varied case material and the literature reports, that we can divide the war neuroses into acute cases and chronic ones. The acute cases show a different symptomatology than those which run a prolonged course. The acute cases of war neuroses can again be roughly divided into two groups: Those cases in which a neurosis develops suddenly, and those in which it develops rather slowly. There are naturally no clearly-defined boundary lines. Nevertheless, in the majority of the cases the above-mentioned classification can be employed. The acute cases of war neuroses show different clinical pictures. We encounter four main groups: First, the fatigue and exhaustion states; second, the anxiety types; third, the obsessive compulsives; and fourth, the cases which display primarily a psychosomatic syndrome as, for instance, gastric ulcer, asthma, etc. Regardless of the clinical symptomatology we see a common reaction in all of them. The slowly developing cases only show in a more protracted way the manifestations which the acute shock cases display suddenly.

In a previous publication I described that emotional tension has a tremendous impact on the self-government of the individual. It collapses totally or partially, and is replaced by a state of anarchy, which disorganizes the normal balance of excitation and inhibition in the organism. The disintegration of self-government manifests itself in three different ways: in an emotional storm, in a motility storm, and in a vegetative storm. In other words, the patient shows signs of anxiety, terror, amnesia, confusion, hyper- or hypomotility, immobilization or trembling, and, what is very important, the vegetative nervous system is practically always involved, showing an alteration in the sleep function, increased perspiration, changes in the regulative mechanisms of the heart, bowels, etc.

* Read December 14, 1943 at the joint meeting of The New York Neurological Society and the Section of Neurology and Psychiatry of The New York Academy of Medicine.

We emphasized that this phase of the war neuroses subsides in a majority of the cases, if the patient receives proper rest, food and sedation, and if he is removed from the danger zone. These states, which are very similar to the old fatigue or exhaustion states, encountered following a marked emotional upset or after a debilitating physical disease, recover very quickly. This first anxiety phase of the traumatic neuroses is a psychosomatic entity. It is most likely that in such a state a dissociation occurs between the cortical activity and the subcortical emotional and vegetative regulative functions. We have a state of diaschisis. This would explain many of the symptoms of the acute war neuroses, the hyper- or hypo-excitability, the lack of emotional control, the inability to select stimuli, but to respond totally to every little stimulus, which is in no relationship to the total response directed toward it. It also explains a dissociation of the vegetative control and the heightened tendency of the individual to convert emotional manifestations into a vegetative function.

We also emphasized that the traumatic war neuroses not only profoundly disturb the mental integration of the individual, but also his physiological function, and we have to look upon emotion which provokes a disturbance not only as a psychic mechanism, but also as a somatic one. In this sense the older idea that the shock does something to the organism which is more than mental is essentially correct. If we assume that fear is the basic mechanism in all traumatic war neuroses, we have to realize that fear is one of the most potent physiological disorganizers known, which furthermore tend to get conditioned.

After the first phase of the traumatic war neuroses many of the patients who do not recover enter into the second phase of the anxiety state, in which the constitutional disposition of the person plays quite a role. In the second phase, the acute anxiety and somatic manifestations are fused with old infantile fear and anxiety structures. The treatment, in our opinion, has to interpose itself between these two layers, and to prevent an amalgamation of these two phases of anxiety. We see that in individuals in whom infantile fear is not very marked, and in whom the neurosis is strongly externalized, the treatment succeeds rather quickly, whereas in others, deep-rooted fear mechanisms become activated, and in many instances the treatment becomes difficult.

In the treatment of the traumatic war neuroses many different methods were used. The treatment could be subdivided into supportive,

suggestive, hypnotic and into analytical forms. In addition, in the last war and in this war, group treatments were used. It is obvious that in the hands of skilled persons, each of these treatments yields results. We personally preferred, in the acute cases, the treatment which could be called narcosuggestive or narcocathartic.

We believe that sedation plays a great role in preventing the development of more serious states of war neuroses, if it is properly applied in the acute state.

We especially preferred to conduct the psychotherapeutic procedure in connection with the sedation because it facilitated the psychotherapy. It was much easier to suggest to a relaxed and sedated individual that many of his fears and vegetative dysfunctions would disappear. We applied this narcosuggestive treatment in the following manner. The patient had an initial interview, during which all the material was gathered concerning the war experience. His previous attitudes, his general emotional organization, his physical and mental make-up, were sized up. He was then reassured that his symptoms, as, for instance, insomnia, jitteriness, anorexia, would be quickly relieved. Incidentally, this reassurance was reinforced quite strongly by other successfully treated patients.

After the initial interview, a sodium amytal interview was conducted. In this instance we injected 3 to 5 cc. sodium amytal intravenously. The injection should be given slowly. The amount depends on the patient's reaction. The optimum dose of sodium amytal produces a state of relaxation, the patient is somewhat drowsy, he says he feels as relaxed as though he were about to sleep. In some patients actual "twilight sleep" can be produced. The drug should not be given in sleep-producing amounts. When the patient is relaxed and at ease, we ask him about his traumatic experiences, and after a while we let him talk freely. This interview is partly a spontaneous and partly a directed one. If the material uncovered during this interview indicates that the conscious traumatic experience of the patient is about the same as was obtained in the initial interview, he is marked for suggestive treatment. In the same way, if the patient expresses a wish to forget his experiences, and does not ruminate on his traumatic memory material, he is again a candidate for a suggestive treatment. If, however, the patient in the sodium amytal interview produces a large amount of material which was not reported at the initial interview, or

if the patient is preoccupied to regain repressed material, he will do best if a narcocathartic treatment is given. If narcosuggestion is used, it is pointed out to the patient that he is now relaxed, quiet, that the action of his heart is normal, that he doesn't perspire, and that the doctor is capable of stopping his overirritation. He also receives short and pointed explanations about the genesis of his symptoms, and he is reassured about his anxiety conflicts. Such a treatment can be carried out in a few minutes in connection with the injections of sodium amytal. At the end of this treatment it is suggested that the patient should sleep. Such a treatment is carried out about three to four times a week. If necessary, it can be given more often.

In the narcocathartic form of treatment, after injection of the sodium amytal, the patient is asked to tell his experiences. He generally will start off with some conscious war experience, and then he will continue to talk about other repressed material. Free association is used, but not entirely freely. If the patient should bring in material which is felt to have no connection with his sickness, he is pressed back to the war experience. With this type of treatment in the acute cases of war neuroses, it is not very essential to follow the indicated clue back into childhood experiences. In the more chronic cases of war neuroses, where a more analytical procedure is followed, this will be necessary.

The narcocathartic treatment session lasts at least half an hour. At the end of it, the same suggestions should again be given as in the narcosuggestive treatment. This form of treatment should be given about three times a week. The gathered material should be explained to the patient. This can be given in a non-sedated state.

The narcocathartic type of treatment brings us to a theoretical consideration. In most of the text-books on war neuroses, it is mentioned that the conflict between duty and self-preservation is productive of anxiety. It is also mentioned that if the patient produces the repressed material in connection with the traumatic experience, his symptoms will cease. We have no objection to the first explanation, even though we feel that self-preservation alone could produce anxiety states without a conflict concerning duty. In acute anxiety states of civilians who were in a panic, the sense of duty didn't even enter into the picture.

The second contention, that the treatment has to concentrate on releasing repressed material, is a too generalized assumption. A large number of our patients were fully conscious of what they went through.

That a considerable layer of the experiences are conscious is probably the reason why many cases of war neuroses respond quickly to therapy, in contrast with the ordinary peacetime neuroses.

In another group of patients, however, the production of the repressed material, the emotional abreaction, undeniably facilitated the cure. In many instances, patients who wanted to forget the traumatic experience, who didn't even want to dwell on it, who merely wanted a relief from the overaction of the nervous system, fared best, while patients in whom repressed material had to be brought back did not do so well. I presume that most of the chronic cases belong to this second group, while the first group, which were simple anxiety or fatigue states, are largely overcome by themselves. Patients who ruminate in a retrograde way about traumatic experiences belong to the group which wanted to forget. Patients who worry a great deal as to what would happen to them if they go back belong mainly in the group which wanted to know everything, to what dangers they were exposed, what they went through; these broodings often reinforced some of their traumatic fears.

We believe that the quieting of the vegetative nervous system, the possibility of diminishing the emotional push which is behind the anxiety state, is largely responsible for the effectiveness of the amytal treatment.

Another important factor in this treatment is the fact that the patient actually experiences on his own body the promises of the cure rather quickly before a conditioning sets in, and before he despairs of being able to overcome his anxieties. The treatment can be given rapidly, and a fairly large number of patients can be treated simultaneously. With hypnosis very similar results can be obtained, but the more intractable type of patients do not respond to it.

Another advantage of this treatment is that it can be used even in those cases in which confusion, amnesia and hysterical paralysis coexist. These patients generally do not benefit by supportive treatment alone, or by group treatment. They expect that something physical will be done to them. They do not consider the physician who simply talks to them as a therapist.

The psychosomatic treatment of the traumatic war neuroses is probably the most effective one in our experience, and I think it should be used widely and almost immediately after the patient is admitted to a hospital. That means that the cases should be treated close to the place

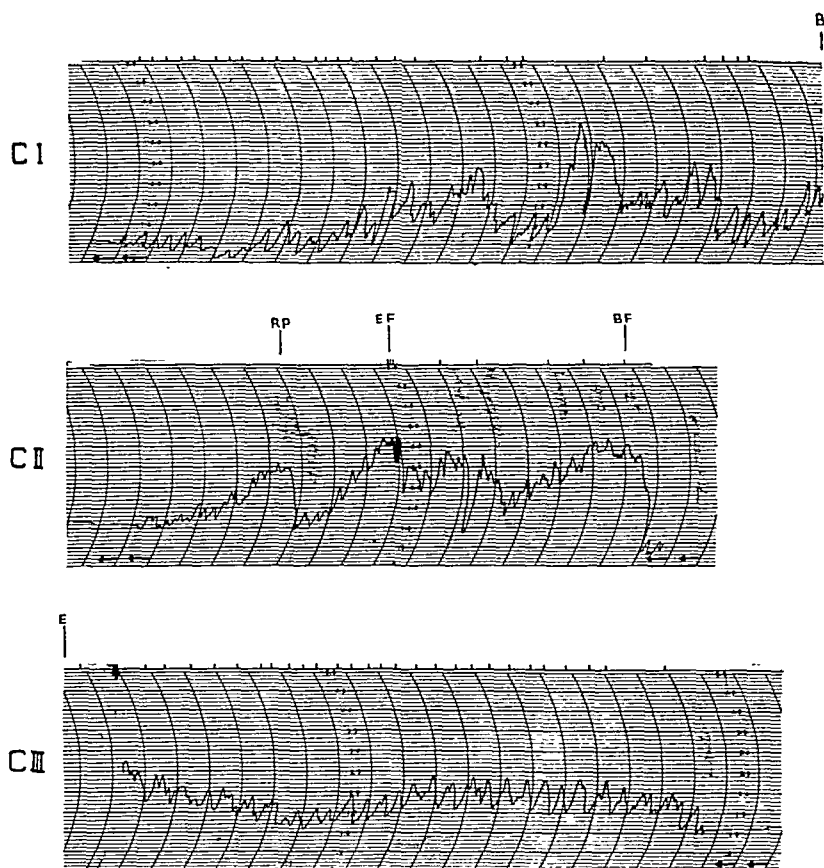


Figure 1

- I. Before sound film: Simple questions asked
 - II. During sound film: Sound film of torpedoing shown
 - III. After sound film: Simple questions repeated
 - B. Beginning of record
 - BF. Beginning of sound film
 - E. End of record
 - EF. End of sound film
 - RP. Recovery point after the showing of sound film
- The RP. is the point at which the individual returns to the approximate level of electrical resistance with which he began at BF.
- This record indicates a quick "emotional" recovery of the patient after seeing the sound film. The distance between EF. and RP. took about 50 seconds.

where the war neurosis developed, and that the treatment should not be postponed a few weeks or months until the patient is brought back home, because during the elapsed time the best therapeutic opportunities are missed and the anxiety mechanisms become conditioned.

We believe that with these comparatively simple methods of treatment, if applied quickly and skillfully, about 75 per cent of the patients

could be restored to normal mental health.

In practically all cases of war neuroses emotional tension can be detected. This tension is a forerunner or a concomitant of anxiety. It is obvious that this tension is expressed differently by various individuals. The premorbid, emotional organization of the patient, pathoplastically influences the overt expression of nervous tension. The feeling of tension is the first symptom which occurs in all types of war neuroses, and it is practically the last symptom which disappears. The "jittery" feeling is present in the slowly developing fatigue state as well as in the acute "terror" or "shock" cases. In the latter it is often covered by the more dramatic and conspicuous symptoms of agitation, amnesia, or hysterical manifestations. When these symptoms disappear the patients still complain about being tense, jumpy, highstrung.

We do not want to discuss at present the relationship between tension and anxiety. In our opinion they are intimately related. The tension is the expression of a sustained overalertness of the nervous system, most likely originally devised to deal with self-preservation. Due to the intimate relationship between emotional tension and vegetative nervous system function, repeated attempts were made to register emotion indirectly at its somatic end. The registration of the heart beat, blood pressure, pulse rate and respiration were all tried in connection with different emotional states. It is also known for a long time that the electrical resistance of a person changes under emotional stress, and that it is possible to register the fluctuation of this resistance. The so-called "lie-detector" techniques are based on this principle.

Utilizing this basic idea, we developed a technique to demonstrate the emotional tension in patients suffering from war neuroses. We found the psychogalvanic registration simpler and more reliable than the registration of the blood pressure, which in many cases shows an increase of the systolic readings, but it fluctuates quite markedly in the same patient, and for that reason is quite unreliable.

The galvanometric instrument used is a two-stage direct current amplifying system, connected with an Esterline-Angus Ink Recording Milliammeter. The electric circuit was developed by Fordham University and was used extensively in experimental and criminological work. We also used it on psychotic patients. In all this work I had the collaboration of Drs. Kubis and Rouke of the Department of Psychology, Fordham University. The patients examined were all from the

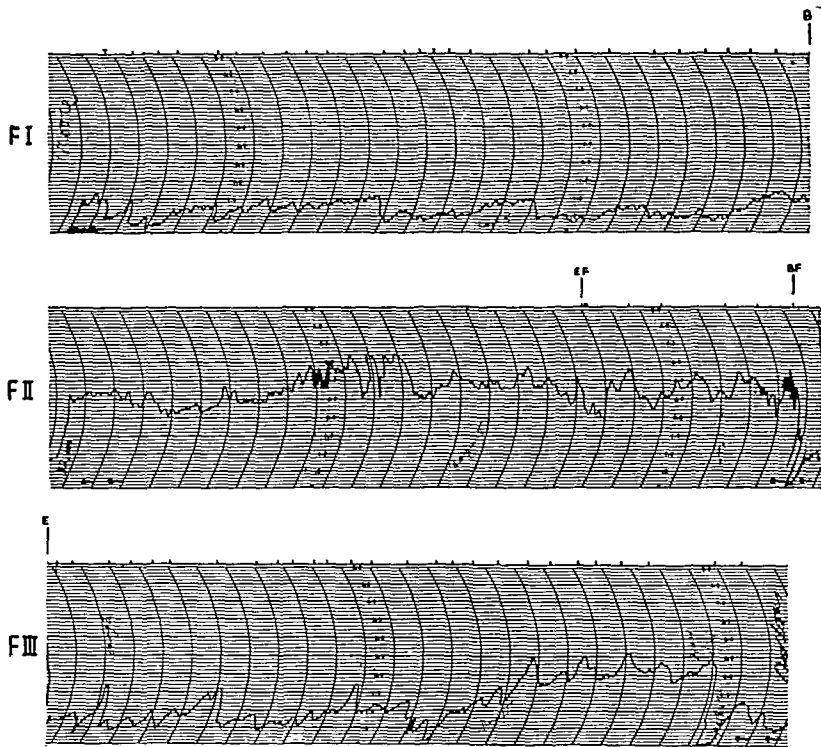


Figure 2

This is the record of a patient with an active traumatic neurosis. There is a sustained emotional tension. No RP. Record discontinued after 4½ minutes.

Merchant Marine Rest Center, Gladstone, N. J., suffering from acute or subacute states of "war nerves." No chronic cases were tested. Besides the patients suffering from war neuroses we used as controls about the same number of patients who had no war neuroses; furthermore, nurses, Red Cross ambulance drivers, and stenographers.

The experiments were carried out in the following manner. Electrodes fitting the palm of each hand were fastened on the patient and connected with the instrument. During the whole examination a running psychogalvanic record was kept. After applying the electrodes a number of questions were asked, which were generally insignificant and did not directly allude to a traumatic war experience. The patient was asked to tell his name, age, and how he felt. During this questioning the initial tension level was ascertained, which is naturally different in various individuals. Some patients are apprehensive, not knowing the procedure, and show an increased emotional tension. It was found

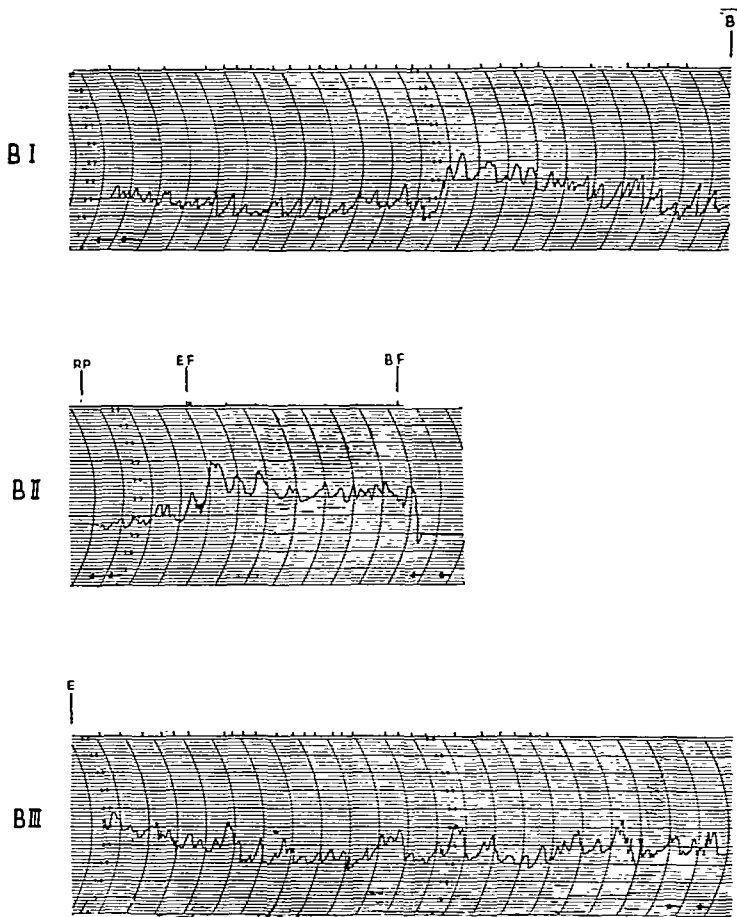


Figure 3

Recovered patient. Distance between EF. and RP. represents a time interval of 1 minute.

that the persons who had no traumatic war experience responded according to their nervous constitution. Some of them showed an immediate apprehension and an increased deflection in the galvanometer. Others remained calm and the deflection of the galvanometer was not marked. When the original tension level was ascertained, a sound film was shown for a few minutes. This film shows a tanker moving peacefully, and depicts every-day activities on board. Then suddenly the ship is torpedoed and sinking. People are hurt, some are jumping overboard to try to save themselves. The picture is quite realistic and is accompanied with impressive sound effects. Several minutes after showing this picture the same initially asked questions are repeated. As you

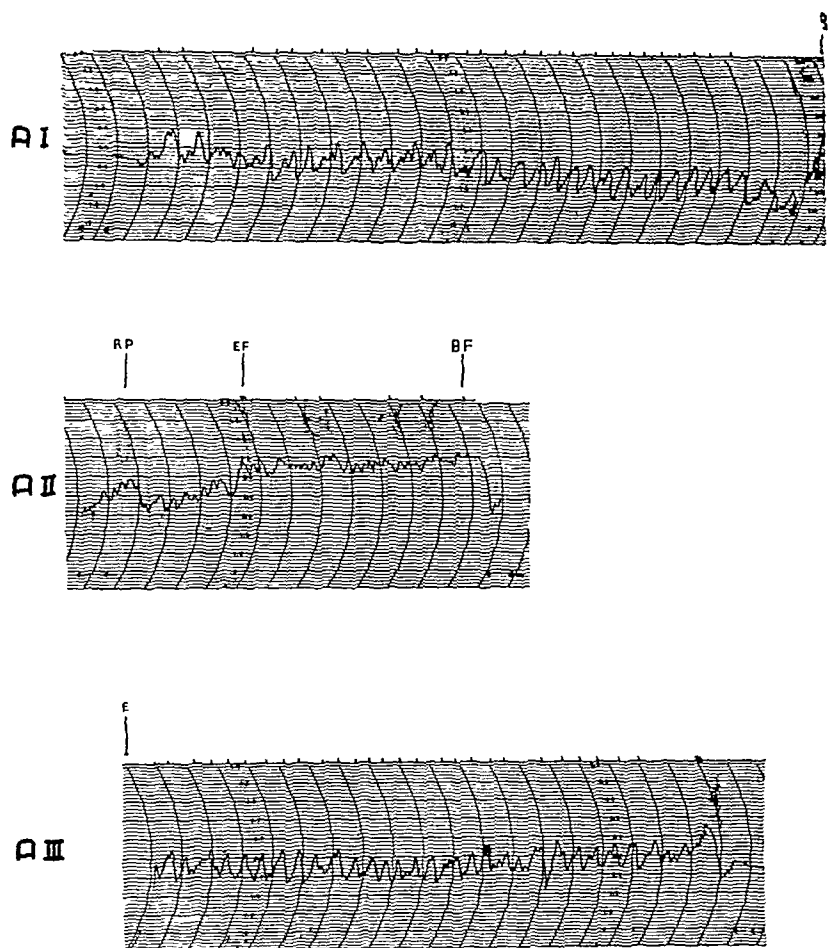


Figure 4

Recovered patient. Distance between EF. and RP represents a time interval of 1 minute.

readily see in the graphs, most persons show an increased emotional tension when the torpedoing occurs. The deflection of the curve upward from the original line is clearly visible. The height of this deflection, however, is not so important. Generally speaking, war neuroses cases show a more marked jumping upward, but occasionally the same condition prevails in impressionable non-war cases. A very significant finding, however, is the duration of the tension state. In an emotionally well-balanced individual, after being shown the picture, the tension quickly dies down. In about $1\frac{1}{2}$ minutes the galvanometer deflection moves downward and reaches the original starting level. In some borderline cases the reaction doesn't return to norm before two minutes.

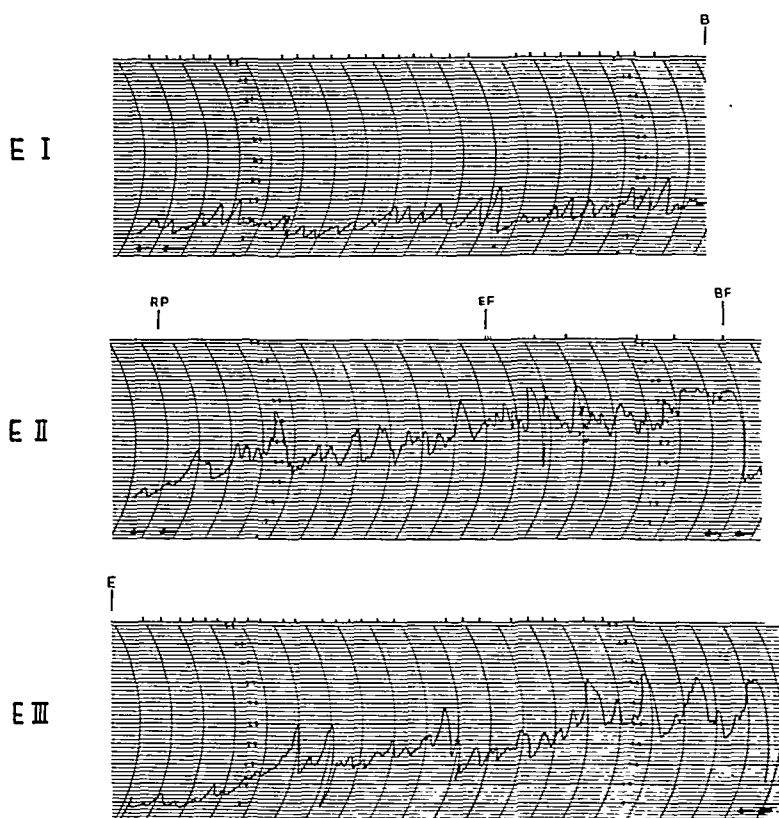


Figure 5

Improved patient. Residuals of neurosis present. Distance between EF. and RP. represents a time interval of $2\frac{1}{2}$ minutes (normal $1\frac{1}{2}$ minutes).

If after two minutes the needle of the galvanometer still does not drop down, a protracted tension state is present. In some instances we had to wait several minutes until the reaction died down. In several severe cases of war neuroses the needle stayed up so long that by the conclusion of the experiment, still no relaxation of the tension occurred. In our experience non-war cases, including neurotic individuals, always came down in about two minutes. Apparently the moving picture does not involve them emotionally too much. Only some tension occurs, but it rapidly diminishes and the original emotional balance is restored. It is quite different, however, with cases suffering from war neuroses. In these cases a protracted tension state is invariably demonstrable. In most instances the galvanometric record runs parallel with the clinical observation. The person is obviously tense, jittery, at times shows

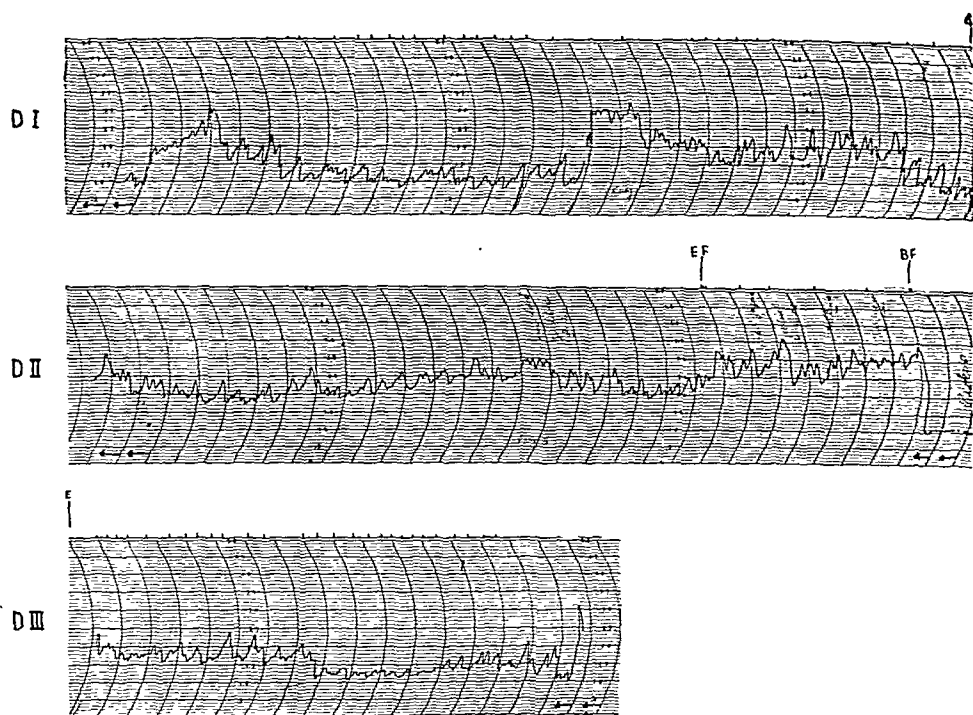


Figure 6

Unimproved patient. Tension sustained after EF. No RP.

tremor, and readily admits a subjective feeling of tension or anxiety. In a number of instances, however, the psychogalvanometric recording is superior to the clinical observation or subjective statement of the patient. We had cases of war neuroses where the patient appeared to be clinically well and was ready to resume his duties. The psychogalvanometer, however, still indicated the presence of apprehension. In some instances a relapse occurred in these patients.

It was noticed by a number of investigators that patients suffering from gross hysterical manifestations as, for instance, hysterical paralysis or deafness, did not display much anxiety; on the contrary, they appeared to be rather happy and content. The emotional tension is clearly demonstrable in these patients with the psychogalvanometer.

In some patients who suffered from gastric ulcer which developed as a result of war experience, no overt anxiety is demonstrable. They disclaimed that they were anxious or apprehensive. Our psychogalvanometric records, however, clearly show a marked apprehension in these patients. We think, therefore, that the psychogalvanometric recording

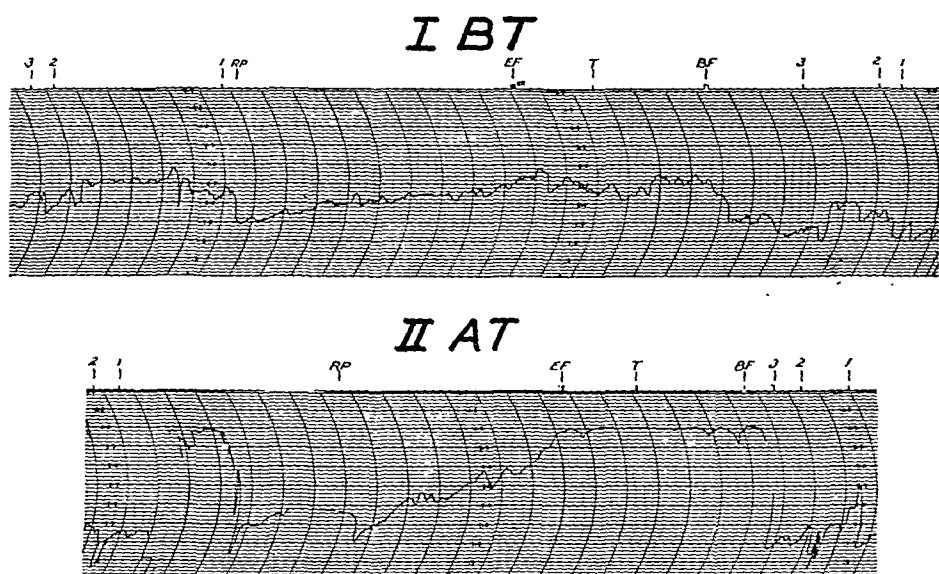


Figure 7

- I. BT. Before treatment session with sodium amytal and psychotherapy. Distance between EF. and RP. represents a time interval of 2 minutes and 20 seconds.
- II. AT. After treatment session. Distance between EF. and RP. represents a time interval of one minute and 50 seconds.

gives quite a good objective evidence as to whether or not apprehension is present.

Seemingly in persons who developed a traumatic war neurosis the showing of a picture which depicts situations to which they were exposed mobilizes a great deal of associative material, which produces apprehension, anxiety and its vegetative concomitants. In individuals who did not have such an experience the picture is meaningless and does not produce an emotional upheaval. We believed in the beginning that the persons who were exposed to this picture would not respond in the same way when they saw it again the second or third time. Apparently no emotional adaptation occurred. The persons who remained jittery and apprehensive responded over and over again in a similar way as when they first saw the picture. Only when they felt relaxed and the clinical symptoms of the neurosis disappeared, did they show a normal form of response. It is naturally possible that if a person is exposed to the same stimulus very often, he will not respond to it because a conditioning takes place. In such an instance, not the identical

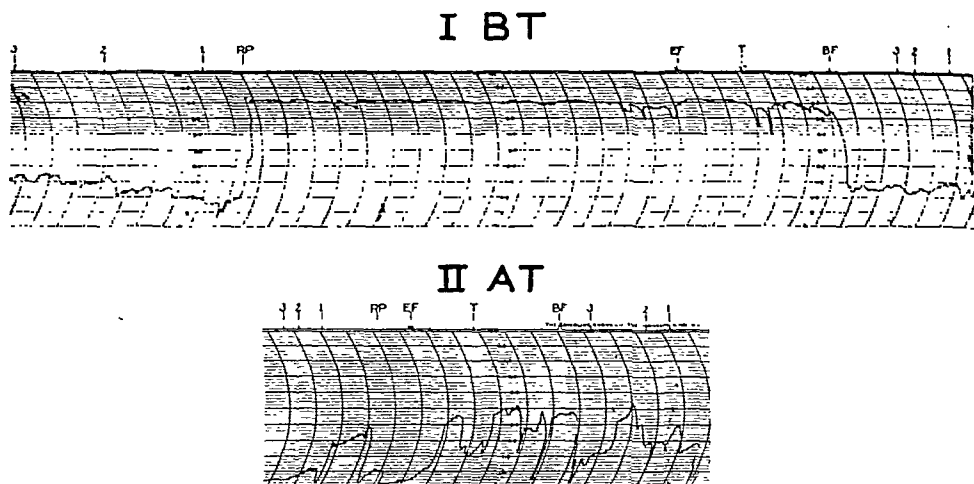


Figure 8

- I. BT. Before treatment session with sodium amytal and psychotherapy. Distance between EF. and RP. represents a time interval of 4 minutes.
- II. AT. After treatment session. Distance between EF. and RP. represents a time interval of 30 seconds.

but similar pictures should be shown.

In quite a large number of patients suffering from traumatic war neuroses we took a record when they were admitted to the Rest Home. Later on we took it again when the treatment progressed after a while, and finally, a retake was made before discharge. Those patients who showed a good recovery clinically, invariably demonstrated a psychogalvanic response which returned to normal, or, at least, the record became borderline. We believe, therefore, that the recovery of the patient could be measured with this test, and the state of his emotional relaxation objectively recorded. How far this test can be used for a long-run prognostication in the traumatic war neuroses we do not know. We had two patients who showed a good clinical recovery and a normal psychogalvanic record, who some time after discharge relapsed. It is possible that when the patient is again exposed to some experience which reactivates the fear mechanism suddenly, the full picture of the neurosis can be reactivated in a short time. This so-called associative reactivation is an interesting phenomenon, and was discussed by many authors. In the majority of our patients, however, we had the impression that after they recovered they remained well. We naturally do not know whether or not they were ever exposed to a similar war experience.

The psychogalvanic test can be also utilized for therapeutic investigations. We used it to demonstrate the influence of narcosuggestion and narcoanalysis. It naturally can be used to test the efficacy of any other method of treatment. One of our graphs shows that under the influence of sodium amytal and suggestion, the patient who for a short time before showed a marked tension became nearly normal in his psychogalvanic reaction while under treatment. Correspondingly, he also showed a clinical improvement. We believe that this method objectively demonstrates how the drug or psychotherapeutic procedures relax the anxiety, and naturally also eliminate the vegetative nervous system reverberations of the emotional tension. We believe it also shows clearly how important the sedation is in the war neuroses. The amount of sodium amytal in these cases naturally is only a sedative dose, or one which produces relaxation and a twilight state, but not a dose which produces sleep. If a high dose of sodium amytal, which leads to sleep, is given, it is natural that no psychogalvanic response will occur. In some patients some prognostication is possible as to the length of duration of treatment. If following a session with sodium amytal and psychotherapy a patient remains free from tension for several hours, the prognosis for quick recovery is rather good. In the more intractable cases of war neuroses, even though a relaxation occurred during the treatment, the old apprehension is back after a short time.

The psychogalvanometric assay of the patient can be given quickly. The test can be completed in a few minutes, which we believe is of an advantage. From a theoretical point of view we are impressed by the fact that a basic uniform deviation seems to be present in all the war cases, regardless of their clinical symptomatology, which would indicate that the apprehension and tension and its vegetative manifestations are the common denominators in all the war neuroses, and the other rather complicated clinical pictures are only secondary elaborations on this basic psychosomatic alteration.

PROGRESS IN SULFONAMIDE PROPHYLAXIS OF ACUTE INFECTIOUS DISEASES*

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SULFONAMIDE drugs are reported to be effective in the prevention of some of the infectious diseases caused by sulfonamide susceptible microorganisms. Many of the reports state that extensive studies are necessary to determine the effectiveness and hazards of such prophylactic treatment before the procedure can become a regular part of public health practice. I hope that this need for assembling the largest possible experience will justify in some measure the reporting of results entirely based on the work of others. Your indulgence is requested to present a review which is only a reflection of the specific data and opinions of the many physicians who made the observations. I am greatly indebted to all those whose publications are reviewed.

Studies were found that showed the extent of the collective experience with sulfonamide drug prevention of rheumatic fever recurrences, scarlet fever, upper respiratory infections, gonorrhea, chancroid, meningococcus meningitis and bacillary dysentery.

The prevention of bacterial complications by treatment during the course of infections such as scarlet fever, measles, pertussis, otitis media and upper respiratory infections was not included in this group.

Rheumatic fever recurrences—The prevention of rheumatic fever recurrences has been studied more thoroughly than any other prophylactic use of sulfonamide drugs. Eight studies¹⁻⁸ were reviewed of which four were well controlled and sufficiently large to give reliable results. In four comparatively large studies six recurrences of rheumatic fever occurred in 306 patients treated for one season each and seventy recurrences occurred in 341 control patients observed for one season each. The rate of recurrences was eleven times as great in the controls as in

* Read December 21, 1943 before the Section of Medicine of The New York Academy of Medicine.

the treated cases, and it is therefore apparent that a substantial degree of prevention was conferred by treatment.

The precautions observed in the selection of patients and the completeness of the observations were sufficient to make the results significant. Only patients who showed no signs of active infection were treated because the administration of sulfanilamide has been found to be without therapeutic effect and possibly harmful in acute attacks of rheumatic fever. The treated groups and control groups were generally similar in age distribution, duration of rheumatic state, severity of rheumatic fever attacks and cardiac involvement in all four studies and therefore similar in their tendency to recurrence of active infection. Cases that stopped taking sulfanilamide were placed in the control group in one of the studies, and recurrences occurred in such cases with the same frequency as in those who had never had the drug.

Sulfanilamide was administered daily in all the studies throughout the winter and spring months, and in some cases throughout the year for from one season to four years in the same patients. The dosage varied from 0.6 gram per day to 3 grams per day. Blood level determinations indicated that a fairly constant concentration of the drug was maintained by doses at twelve hourly intervals and a level of 1-2 mg. per cent was sought. Difficulties in administration with the exception of toxic reactions were confined to those inherent in conscientious observance of any schedule of continuous medication.

Progressive changes in cardiac involvement particularly the size of the heart were followed throughout the period of observation by Hansen, Platou and Dwan.⁵ Increase in size of the heart was more frequent in the controls and decrease in size was more frequent in the treated cases. More data on this point are needed.

The regular occurrence of hemolytic streptococci of the same type in the throats of patients during the upper respiratory infections preceding rheumatic fever recurrences was clearly demonstrated by Kuttner and Reyersbach.⁷ The cases were treated in a home for rheumatic fever patients and opportunities for acquiring fresh hemolytic streptococcal infection were confined almost entirely to other patients and staff. Type 15 (Lancefield) streptococci were found in all cases suffering from active rheumatic infection in the first year of the study and type 36 (Lancefield) in the second year. In the control series a majority of patients that carried the predominant strain in the epidemic had

upper respiratory infections and recurrences. In the treated series a substantial number of patients yielded cultures of strains predominating in the epidemic but nearly all escaped both upper respiratory infections and rheumatic recurrences. The results of cultures indicated that sulfanilamide may have some effect in preventing the acquisition of streptococci or possibly some effect on the length of time that acquired streptococci are retained, but this was not clear. It is evident that sulfanilamide does prevent streptococcal upper respiratory infections as well as the symptoms of active rheumatic infections in patients who do acquire the strains that predominate in an epidemic.

Scarlet fever: Two reports,^{9,10} of scarlet fever prevention were reviewed, one a large scale controlled study of an epidemic¹⁰ which will be described and an uncontrolled study of a relatively small number of persons in contact with scarlet fever cases.⁹ The first mentioned report by Watson, Schwentker, Fetherston and Rothbard¹⁰ described scarlet fever cases as decreasing during treatment in one group of subjects while continuing at the same level for three weeks in untreated controls. The controls were then treated and scarlet fever cases decreased rapidly, ceased to appear and remained absent during a period of 17 days after treatment of both groups ended.

The subjects of this study by Watson, Schwentker, Fetherston and Rothbard were personnel of a naval training station, who slept and had their meals together. The total number of persons varied and was given as several thousands. The length of stay of individuals also varied from four months for some students to transients some of whom stayed only one week or less. The period from the first case to the end of observation was 103 days. Cases of scarlet fever were recognized at sick call. Diagnosis was confirmed by hospital admission. Bacteriological examinations of throat cultures from cases and sample groups of treated and untreated persons for streptococci showed that type 19 (Lancefield) was associated with scarlet fever. The number harboring type 19 did not change appreciably during the sulfonamide treatment.

Sulfadiazine was administered in doses of 1 gram per day for thirty-two days in the first treated group and for twelve days in the second treated group and was discontinued for both groups on the same day. No serious toxic effects occurred. Only three skin rashes caused by the drug were reported.

The opinion of the authors was unequivocal that further progress

of the epidemic of scarlet fever was prevented by the use of sulfadiazine.

Upper respiratory infections: Only one study primarily concerned with the prophylaxis of upper respiratory infections was found but two other studies contained some data on upper respiratory infections. There is no reason to believe that any of the great majority of upper respiratory infections which are caused by filterable viruses may be prevented by sulfonamide therapy, and these studies were therefore directed to the prevention of upper respiratory infections of types usually caused by hemolytic streptococci.

Garson¹¹ administered 2.75 grams of sulfanilamide in lozenges in fourteen days to new recruits in a military camp. Two per cent of the treated soldiers as compared with 10 per cent of the untreated had tonsillitis. Other upper respiratory infections were influenced only slightly.

In the rheumatic fever study of Kuttner et al⁷ upper respiratory infections in which the type of streptococcus predominating in the epidemic was isolated almost disappeared in the treated cases while remaining about the expected rate in the untreated.

During the study of the prophylaxis of scarlet fever by Watson, Schwentker, Fetherston and Rothbard¹⁰ mentioned above the average daily number of sick calls with respiratory complaints was reduced to about one half the previous number during periods of treatment while other complaints were not affected.

All three studies show that the prevention of upper respiratory infections when a substantial proportion are caused by streptococcus merits special study.

Gonorrhea: The prompt disappearance of gonococci from the urethra of patients treated with sulfathiazole has suggested that small doses at the time of exposure to infection would have prophylactic effect. Four reports^{12, 13, 14, 15} were found of sulfathiazole used for gonorrhea prophylaxis two of which were controlled. All were apparently successful and all were provisional in that further work was contemplated. The two controlled studies were carried out by the medical staffs of Negro troops in camps in the U.S.A. In one, by Loveless and Denton,¹⁴ 3 doses of 2 grams each of sulfathiazole were given, one before and two after leave to an average population of 1,400 troops during five months with a resulting decrease in the gonorrhea cases to a rate

of eight cases of gonorrhea per thousand per year, compared with a rate of 171 per thousand per year in 4,000 untreated troops in the same camp in the same period. In the second controlled study by Arthur and Derrmon¹⁵ the administration of 6 grams of sulfathiazole in three doses the day after 199 exposures entirely prevented the occurrence of acute urethritis as compared with 384 exposures without treatment in the same camp, in the same period which were followed by an attack rate of 39 cases of gonorrhea per thousand exposures. Only a few cases of nausea and 2 cases of mild gastric upsets attributed to toxic effects of sulfathiazole were noted.

Chancroid: Chancroid is also readily cured with sulfathiazole and the prophylactic effect was studied in the same two controlled studies of gonorrhea prophylaxis. A rate of six cases of chancroid per thousand per year in the treated group as compared with 52 per thousand per year among the controls was found in the first study and rates of 5 per thousand exposures in the treated troops as compared with 47 per thousand exposures were found in the second study. During both studies the rates for syphilis were relatively unaffected in treated cases as compared with controls. In one study primary lesions did not occur among the treated persons and it was suggested that sulfathiazole may inhibit the tissue reaction without preventing infection.

Meningococcus meningitis and the meningococcus carrier state: The number of deaths from meningococcus meningitis is relatively small during this epidemic period as compared with other epidemic periods because of the effectiveness of sulfonamide treatment of cases. The progress of the epidemic has not been influenced by treatment, however, and prevention through sulfonamide prophylaxis has been extensively studied with the object of halting the epidemic. Ten reports¹⁶⁻²⁵ have been made, most of them when only sulfanilamide was available. Sulfanilamide was apparently effective in the cure of carriers but less effective than newer drugs. Four recent studies using sulfapyridine or sulfadiazine were comparatively large in scale and controlled. The carriers were almost completely eliminated in these four studies. There was a tendency for the reappearance of higher carrier rates after three weeks in one study and after longer periods in others, which was least marked in the groups that were best isolated.

Only one of the studies, that of Kuhns et al.,²⁵ included controlled observations of the incidence of meningococcus meningitis. Two cases

of meningitis occurred among 15,000 treated persons and 40 cases among 18,000 controls. The increased incidence of meningitis cases began later in the control groups and subsided as rapidly in one of the control groups as in the corresponding treated group. Since the difference in the number of cases in control and treated groups may have been due to fluctuations in the epidemic independent of treatment it does not offer a sound basis for evaluating the degree of control of the disease.

The subjects were soldiers in relatively permanent encampments in three of the controlled studies and were not described in the other. The groups were not closed to contact with other groups and therefore had opportunities to acquire meningococcic infection after treatment. Such opportunities were at a minimum in the largest study because it included several camps and all the persons in certain camps were treated. Both the treated and control groups in each study contained unusually large percentages of persons who were carriers of meningococci and were generally similar in other respects. Type 1 meningococci were responsible for nearly all cases of disease and type 1 carriers were considered separately in three of the studies. Temporary interference with meningococcus growth by sulfonamide drug in the specimen was avoided by taking cultures after drug administration was stopped and by the addition of para-amino benzoic acid to media.

Sulfadiazine was used in 3 of the larger studies and sulfapyridine was used in one.²⁰ Only 4 to 9 grams per person given in two or three days were required for satisfactory control of meningococcus carriers, and the results were as good with the smallest amount as they were with the largest. Toxic reactions were correspondingly slight. Toxicity was not discussed in two of the studies. Toxic reactions to sulfadiazine were not noted in one study by Cheever, Breese and Upham.²⁴ In the other, by Kuhns et al,²⁵ of 8,000 treated soldiers given 9 grams of sulfadiazine in two days, 10 per cent had subjective complaints and 2 soldiers had skin rashes while among 7,000 soldiers given 4 grams of sulfadiazine in two days the reactions were said to be very few in number.

Bacillary dysentery: Sulfonamide treatment of bacillary dysentery cases reduces the incidence and the duration of the subsequent carrier state for certain strains of the microorganisms. Two studies were found among the ten²⁶⁻³⁵ that were reviewed that reported the treatment of cases and carriers in a closed population and compared the results with

TABLE I

CONTROLLED STUDIES OF SULFONAMIDE PROPHYLAXIS OF
ACUTE INFECTIONS THRU NOVEMBER 1943

| Diseases. Number of Studies. Units used in reporting infections. | Number of Subjects | | Results: Number or Rate of Infections | | Control Times Treated |
|--|---------------------------|-------------------------|---------------------------------------|----------------------------|-----------------------|
| | Treated | Controls | Treated | Controls | |
| <i>Rheumatic Fever Recurrences.</i> 4 Studies. Season-Cases. | 306 | 341 | 6 (2%) | 70 (20.5%) | 11X |
| <i>Scarlet Fever.</i> 1 Study. | | Not given | 9 | 86 | |
| <i>Upper Respiratory Infections.</i> 3 Studies. (a) Tonsillitis. (b) Strep. pharyngitis Season - Cases. (c) Average daily respiratory sick calls. | (a) 322 (b) 108 (c) | 452 104 Not given | 6 (2%) 2 (2%) 29 | 45 (10%) 48 (46%) 61 | 5X 23X 2X |
| <i>Gonorrhea.</i> 2 Studies. (a) Infections per M per annum. (b) Infections per M exposures. | (a) 1,400 (b) 199 | 4,000 384 | 8 0 | 171 39 | 21X |
| <i>Chancroid.</i> 2 Studies. (a) Infections per M per annum. (b) Infections per M exposures. | (a) 1,400 (b) 199 | 4,000 384 | 6 5 | 52 47 | 9X 10X |
| <i>Meningococcus Meningitis.</i> 1 Study. | 15,000 | 18,800 | 2 | 40 | 20X |

TABLE II

CONTROLLED STUDIES OF SULFONAMIDE TREATMENT OF
CARRIERS THRU NOVEMBER 1943

| Microorganisms. Number of Subjects and proportion cultured. | Carriers: Percent of Persons Cultured | | | |
|--|---------------------------------------|-------|---------|-------|
| | Treated | | Control | |
| | Before | After | Before | After |
| <i>Meningococcus.</i> 4 Studies. (a) Treated 1 battalion; control 1 battalion. Samples cultured. | 23 | 0 | | 23 |
| (2) Treated 15,000; controls 18,800. Samples cultured for 8 weeks. | 36 | 3 | 31 | 45 |
| (c) Treated 200; controls 200. All cultured. | 68 | 0 | 68 | 70 |
| (d) Treated 203; controls 186. All cultured. | 79 | 0.5 | 58 | 76 |
| <i>Dysentery Bacilli.</i> 2 Studies. Treated 101; controls 67. All cultured through 10 days after treatment; 4 recurrences after 10 days in one study. | 100 | 1.0 | 100 | 60 |

those in untreated controls. Hardy, Watt, Peterson, and Schlosser;²⁶ and Oppen and Hale²⁹ obtained almost complete elimination of dysentery bacilli from the stools of carriers in mental hospitals with widely different amounts of sulfaguanidine. The first workers gave 15 grams daily for from four to ten days, and the second workers gave only 4 grams daily for seven days. Only Flexner and Newcastle types of dysentery bacilli were found in these controlled series. Controls were alternate carriers and cases in the first report and were persons observed in a previous year in the second report. Precautions were taken to ensure that negative cultures were not temporary findings due to sulfaguanidine in the specimens by repeated culturing one to two weeks after the end of treatment in the first and repeated cultures for from 44 to 121 days in the second study. Four recurrences after 15, 16, 27 and 54 days were found in the second study which were permanently cured by another course of treatment. No mention was made of drug toxicity.

A summary of the numerical data on the prevention of infections is given in Table I. Four rheumatic fever studies showed the number of recurrences 11 times as frequent per season-case as in the treated group. One scarlet fever study showed 86 cases before treatment and nine cases after treatment. Each of three studies of upper respiratory infections were expressed in different units. In the first, tonsillitis was five times as frequent among controls as among treated persons given sulfanilamide. In the second, hemolytic streptococcal pharyngitis was 23 times as frequent in control rheumatic fever patients as among treated patients given sulfanilamide. In the third study the average daily number of sick calls for respiratory complaints was twice as great before treatment as they were during a period when sulfadiazine was given daily for the prophylaxis of scarlet fever. Gonorrhea was twenty-one times as frequent in the controls as in treated persons in one study and at least thirty-nine times as frequent in another. Chancroid was nine times as frequent in the controls as among the treated persons in one study and 10 times as frequent in another. Meningococcus meningitis in one study was twenty times as frequent among controls as among those receiving prophylactic treatment.

A similar summary of data from controlled studies of the treatment of the meningococcus and dysentery carrier states is given in Table II. Four studies of groups with meningococcus carrier rates of 23, 36, 68.

and 79 per cent showed almost complete elimination of carriers. Two studies of dysentery bacillus carriers and cases also showed almost complete elimination of carriers.

One may well ask about the application of prophylactic procedures such as these in civilian public health practice. The answer to this question is that not enough is yet known about the dangers of toxic reactions and the danger of increasing the resistance of microorganisms to sulfonamide drugs when administered to large numbers of normal persons to permit large-scale routine application. The selection of groups to undergo prophylactic treatment cannot be made without definite information as to the relative degrees of risk from disease and from treatment. The existence of such hazards has been demonstrated but they have not been fully considered in most of the reports.

The most complete information as to toxic effects has been reported in rheumatic fever studies, and of these Kuttner⁷ working in an institution had unusual opportunities for observation of the cases and gave the most complete description of reactions. During two seasons, 108 season-cases were treated and fifteen persons had symptoms attributed to the toxic action of continuous sulfanilamide treatment. Seven patients had fever, five had skin manifestations and three had leukopenia. All these reactions developed between the fifth day and the thirty-first day of treatment. Although the reactions were not serious treatment was discontinued in all fifteen patients. Such results have not been exactly duplicated, in other rheumatic fever studies. Stowell and Button⁴ found a higher incidence of toxic reactions and described one fatal case of agranulocytosis, possibly due to sulfonamide treatment. Thomas, France and Reichsman³ on the other hand saw few toxic reactions most of which were mild and were able to continue the treatment. Continuous treatment with sulfanilamide using suitable precautions has not been found to lead to undue hazards by the majority of workers.

Kuttner and Reyersbach⁷ carried their observance farther to learn whether cases having toxic reactions continued to be sensitive to sulfanilamide. Treatment was cautiously started again in nine patients who had toxic reactions. Seven of these nine patients had recurrences of toxic symptoms. Subsequent sulfonamide therapy may therefore be dangerous for the susceptible individuals. The appearance of toxic symptoms after continuous treatment for from five to thirty-one days suggests to me and similar experiences have suggested to other physicians

that the patients become susceptible to such reactions as a result of continuous treatment. Thorough study of this possibility is needed in order to complete our knowledge of the toxic effects of prophylactic sulfonamide therapy. It is not necessary to take a pessimistic view of the dangers of sulfonamide sensitization because penicillin and possibly other chemotherapeutic agents will become available for use in the treatment of infections in sensitive individuals.

The resistance of microorganisms of the pharyngeal flora to the bacteriostatic action of sulfadiazine in persons receiving continuous medication with small doses of sulfadiazine was studied by Julianelle and Siegel. These authors have generously given permission to summarize reports that are now in press for this review. In their studies the administration of sulfadiazine continuously over periods of several months led to a striking but temporary decrease in the total incidence of non-pathogenic gram negative diplococci in nasopharyngeal cultures and a decrease in the incidence of certain strains of pneumococci, but no change in incidence of relatively resistant microorganisms such as staphylococci and diphtheria bacilli. Streptococci were not studied. The total incidence of pneumococci did not vary appreciably but the relative incidence of the type strains changed markedly. Tests of gram negative diplococci and pneumococci obtained before treatment showed most to be readily inhibited by sulfadiazine but strains present after 1 to 2 months of treatment were able to grow in high concentrations of sulfadiazine. Since the pneumococci were mouse virulent and of types that are found in pneumonia and did not change in virulence following treatment, the possibility arises that sulfonamide resistant organisms of these and other species may be developed during continuous prophylactic therapy and may result in infections at a later date that are resistant to treatment with sulfonamide drugs. This possibility must be considered in all forms of sulfonamide treatment but particularly in connection with the continuous treatment of large numbers of normals with sulfonamide drugs. Here again as with susceptibility to toxic reactions the availability of other chemotherapeutic agents tends to minimize the importance of the hazards.

When the hazards are well understood sulfonamide prophylaxis promises to be a useful method of control for certain acute infections. Data on the prevention of rheumatic fever with sulfanilamide are relatively complete and encourage its use particularly in groups of patients

under close supervision. The necessity for facilities for the examination of rheumatic fever patients to detect slight degrees of rheumatic activity before the administration of the drug and to ensure continuous administration without excessive hazards will limit its general application. Control of scarlet fever epidemics by small doses of sulfonamide drug in closed groups is suggested by one study. Prophylaxis of upper respiratory infections caused by hemolytic streptococci should be studied further. Application of sulfathiazole to the prophylaxis of gonorrhea and chancroid depends largely on the professional problems involved in making treatment available and encouraging its use. In meningitis treatment of closed groups in periods of epidemic prevalence as in the army appears justified because of the striking effects on the carrier rates. Further data are needed on the control of the disease that is to be expected from control of the carrier state. Bacillary dysentery prophylaxis with sulfonamide drugs may well be used for individual carriers or groups of carriers.

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BULLETIN OF
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JULY 1944

THE CIRCULATION IN TRAUMATIC
SHOCK IN MAN*

Harvey Lecture, February 17, 1944

D. W. RICHARDS, JR.

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College of Physicians and Surgeons, Columbia University

T

HIS lecture is in large part a report of an investigation that has been in progress during the past two years at Bellevue Hospital, a study of the circulation in human cases of injury with shock.*

As is well known, the intensive research on wound shock carried out during and shortly after the last war has provided the foundation of our knowledge of the subject. This large amount of clinical and experimental material was summarized in the now classical monograph by Cannon¹ published in 1923. In this, the traditional division into primary and secondary shock was retained: primary shock, the immediate stunning effect of injury, a neurogenic or vasomotor phenomenon of the nature of syncope; and secondary shock, the more slowly developing but progressive failure, with the characteristic clinical manifestations—weakness, pallor, sweating, thirst, thready pulse, and a progressively falling arterial blood pressure. It was also shown at

* This investigation was carried out under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and Columbia University, with the collaboration of New York University. Additional support for the research was provided by the Commonwealth Fund and the Josiah Macy, Jr., Foundation.

this time that in shock, metabolism is depressed, a state of acidosis exists, and there is diminished oxygen content of the venous blood. Hemoconcentration was believed to be another of the constant features of the shock state.

Perhaps the most fundamental of the new findings established by actual measurement in the course of these wartime investigations, was that secondary shock following injury was regularly associated with a marked loss of total circulating blood volume. It was further postulated, though not proved, that it was this loss of blood volume which in turn led to decreased venous return and diminished volume of flow of blood. The earlier theories of so-called vasomotor exhaustion were found largely untenable, the state of the vascular bed in shock being one of vasoconstriction rather than vasodilatation.

Following a suggestion made by Gesell,² the factors involved in the whole mechanism of shock were divided into two groups, initiating and sustaining factors. The initiating were essentially those that I have just described. The sustaining factors were less definite, but much thought was given to the possible late effects of the products of metabolism, and to toxic substances which might be produced in injured tissues, or derived from uninjured tissues suffering from inadequate circulation.

An active period of investigation began again about 1927 and has continued since. Of a number of excellent recent reviews in which this work has been summarized, one that has been of particular value for us has been the physiological critique and summary by Wiggers,³ published just two years ago. In this he reviewed both what was known, and what was still required to be found out: a number of important facts about the circulation in shock which were well established, both in animals subjected to various types of experimental injury, and in the clinical forms seen in man; certain other things known in animals but not in man; and still other aspects in which there was not satisfactory knowledge of any kind.

As to the mechanism of shock, Wiggers supported the position reached by Cannon in stating categorically that "reduction in the volume of blood returned to the heart is the keystone of all modern conceptions of shock." It was known, as already stated, that total circulating blood volume was reduced. Johnson and Blalock⁴ had demonstrated decrease in volume flow of blood, or cardiac output, in

experimental shock in animals. No data were available in man, as no adequate technique of measurement was available. On the important question of the effective venous return or the inflow pressure of blood at the right auricle, there was also no knowledge in man, and not very much in animals.

The view continued to be widely held that an essential and central feature of traumatic shock is hemoconcentration. Moon,⁵ in particular, supported the theory that a fundamental mechanism producing shock is a general capillary dilatation, with increase in capillary permeability throughout the body and consequent loss of plasma into the tissues. Blalock⁶ and Phemister⁷ strenuously opposed this theory, bringing evidence to show that in experimental shock the decrease in blood volume could be entirely accounted for by the amount of blood or plasma lost at the site of local injury.

If new ground were to be broken in developing further the knowledge of shock, particularly clinical shock in human cases of injury, it was clear that new techniques, new methods of study, were needed. The chief reason that prompted our group, working under Cournand on the Tuberculosis Service at Bellevue Hospital, to undertake an investigation in this field, was the fact that, during the latter part of 1940 and early 1941 we had developed what appeared to be a reliable technique for measuring in man both the pressure of blood in the right auricle, and the total volume flow of blood or cardiac output—measurements which among other things, might provide Wiggers with the keystone which he required to prove in man the current theory of the dynamics of shock.

These measurements were achieved by means of a long ureteral catheter introduced into a median basilic vein and thence passed along axillary and subclavian veins into the right auricle. The technique was not wholly new, having been carried out by Forssmann⁸ (with himself as subject) more than ten years before, and having been used since in some investigations in Germany, France, and Portugal.⁹ It had not, however, been developed systematically as a means of physiological study. With the possible danger of clot and embolus formation, it looked as if it might be a dangerous procedure; and as a matter of fact, we had vacillated for eight years with nothing but a series of somewhat desultory trials in animals, and one unsuccessful attempt in man, to show for it. In the autumn of 1940, Cournand, with Ranges, finally

carried the procedure through successfully. The technique, clumsy at the start, has been perfected especially by Cournand, Riley, and Breed, and has with practice proved to be remarkably easy, safe, and painless, no serious untoward effects having been encountered in over 250 catheterizations.

With this technique it was a simple matter to register the pressure of blood in the right auricle. This is not the true "effective venous return," the latter being the pressure in the right auricle relative to the intrathoracic pressure. However, any *change* in right auricular pressure, as for example when a patient progressed from shock to recovery, would record a corresponding change in venous return, providing no important alteration had occurred in the patient's respiration.

The catheterization of the right auricle also provided a means of obtaining samples of average or mixed venous blood, which could then be analyzed, particularly for respiratory gases. The mixed venous oxygen, moreover, when combined with the arterial oxygen value and the total oxygen absorbed per minute from the inspired air, provided the data needed to calculate cardiac output by the Fick principle.

I have perhaps given too much time to this particular technique; but it is somewhat new and its nature and the extent of its usefulness are not as yet widely known.

In order to obtain a comprehensive description of the circulation many measurements are needed, and it was fortunately possible to bring together three separate research groups,¹⁰ each equipped with special technical methods: a group under Cournand at Bellevue Hospital, responsible for measurements of pulmonary ventilation and respiratory gas exchange, arterial and venous blood gas analyses of various kinds, and the catheterization technique; a group under Gregersen, providing blood volume determination by the use of the dye T-1824; and a group under Dr. Smith, providing optical registration of arterial pressure tracings by the use of the Hamilton manometer; and in a number of cases also carrying out renal clearance studies by Dr. Smith's techniques.

Thus the plan of the study provided for a fairly comprehensive description of the general circulation, and in addition a simultaneous measurement of the state of the circulation in one particular set of vital organs, the kidneys. Table I summarizes the measurements made.

The whole investigation was made possible through the coöpera-

TABLE I
MEASUREMENTS

1. *Pressure*

Arterial pressure (direct, with needle in femoral artery)
Peripheral (arm) venous pressure.
Pressure in right auricle.

2. *Blood volumes*

Plasma volume (dye dilution technique)
Red cell volume (hematocrit)
Plasma protein

3. *Cardiac output* ("direct Fick" method)

4. *Pulmonary ventilation and respiratory gas exchange.*

5. *Renal clearances.*

tion of the Bellevue Hospital Medical Board in making available to us the cases of injury admitted to its surgical services.

Most particularly I should like to mention the working research team under Cournand, both doctors, technical staff, and nurses, who have carried through these studies often under difficult conditions, on week-days, week-ends and holidays, at all hours of the day and night.

The clinical material consisted in the cases of injury admitted to the Bellevue Hospital emergency service. All instances of shock were of the secondary, progressive form.

The actual procedure was as follows: the patient lay on a bed in the supine position throughout the study. Sedative was given if there was restlessness or complaint of pain. An indwelling needle was placed in one femoral artery, another in an arm vein, and the right heart catheterized through a vein in the other arm, the position of the catheter being determined fluoroscopically. The blood volume, cardiac output, and various chemical and dynamic measurements were carried out, followed by the renal clearances. The patient then received treatment, following which usually one or more further sets of measurements were made. The needles and catheter were left in place throughout, the whole study taking on the average from four to eight hours.

The types of injury, and the number of cases of each that have been studied up to the present, are indicated in Table II.

In presenting these measurements in different forms of injury with shock, it will be convenient to take as the prototype the group of cases of skeletal trauma, that is, injury involving serious and usually multiple

TABLE II

CASE MATERIAL, PERIOD FROM MARCH 1942 TO DECEMBER 1943

| <i>Type of injury</i> | <i>No shock</i> | <i>Shock</i> | <i>Total</i> |
|--------------------------------------|-----------------|--------------|--------------|
| Skeletal trauma | 14 | 21 | 35 |
| Chest injury | 0 | 3 | 3 |
| Hemorrhage | | | |
| Gastrointestinal | 3 | 3 | 6 |
| External | 0 | 6 | 6 |
| Abdominal injury | 3 | 7 | 10 |
| Burns | 3 | 12 | 15 |
| Exposure and refrigeration | 0 | 2 | 2 |
| Head injuries | 8 | 0 | 8 |
| Medical cases with shock | 0 | 7 | 7 |
| Totals | 31 | 61 | 92 |

fractures with more or less soft part damage. Other forms of injury will then be compared with this, specifically hemorrhage, abdominal injuries, and burns. Since the purpose at this point is a description of the initial state of shock, the data will include only the initial set of measurements on each case, which were carried out as soon as possible after admission to the hospital.

We have divided the cases of skeletal trauma into those with shock and those without. The assignment of a case to one or the other of these groups was made on the basis of the clinical picture, the various measurements and particularly the clinical course. It was actually not difficult to make this primary differentiation of shock and no-shock cases.

The basic facts about the dynamics of the circulation in the cases with skeletal trauma and the other types of injury are presented in graphic form in Chart 1. This chart is concerned only with circulatory dynamics. Problems of chemical change, anoxia, acidosis, etc., will be considered separately.

On the left are the values for normal subjects, the individual measurements including plasma and whole blood volume, pressure in the right auricle, cardiac output, arterial pressure, and peripheral resistance.

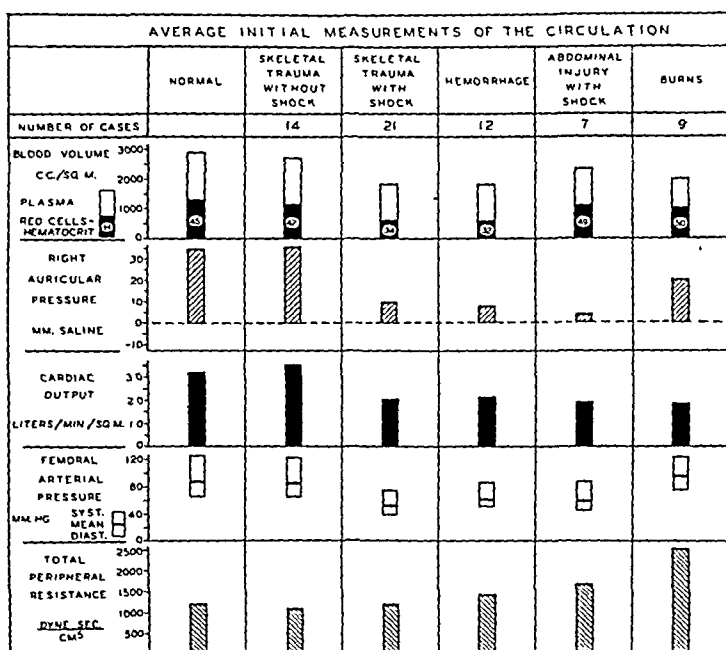


CHART 1

The second column shows similar measurements in fourteen cases of injury without shock, and the third in twenty-one cases of serious injury with shock.

In skeletal trauma without evidence of shock, so far as these measurements were concerned, the circulation was normal, as the chart demonstrates. The blood volume was not significantly decreased, and pressures and blood flow in the general circulation were not impaired. Thus it can be said that in skeletal trauma with no significant loss of blood volume, there was no circulatory failure.

The contrast presented by the cases of skeletal trauma with shock, is striking. The total blood volume was reduced by thirty-five to forty per cent, representing a loss of nearly two liters of blood. The pressure in the right auricle, a relative measure of return flow of blood to the right heart, was reduced by about 25 mm. of water, and the cardiac output diminished by more than one-third. The arterial blood pressure was of course much reduced.

Thus the picture of circulatory failure in acute shock in man, due to skeletal trauma, becomes clear. With the loss of circulating blood volume and drop in arterial pressure there is a failure of venous return

to the heart and corresponding decrease in cardiac output. This is entirely in accord with accepted theory of the circulatory dynamics of shock, as derived from animal studies. The data serve, however, to put the description of this aspect of acute shock in man on a basis of fact rather than of hypothesis.

At the bottom of the chart are given the values for total or over-all peripheral resistance. This is calculated by dividing the mean blood pressure by the cardiac output per second, the ratio indicating the rate of fall of pressure per unit of flow along the vascular system. It will be noted that the average peripheral resistance in shock due to skeletal trauma was normal. Since the total blood volume was much decreased, this suggests that there was a compensatory shrinkage of the vascular bed, and shows that there was an adjustment between the tonus of the vessel wall and the existing blood volume in the regions still actively circulated.

The next group is that of hemorrhage with shock. As will be seen from the chart, the state of circulation in shock due to hemorrhage and in that due to skeletal trauma were closely similar. The average figures of blood volume, auricular pressure, and cardiac output, were, as it happened, almost identical. A difference which may be significant was that arterial blood pressure tended to be less depressed in hemorrhage, and calculated peripheral resistance therefore higher.

Up to this point, so far as concerns the mechanism of shock, the data have kept us in conventional paths. Examination of the figures on blood volume indicates some departure from tradition. It will be noted that both in skeletal trauma and in hemorrhage, the hematocrit was well below normal, and that a state of hemodilution existed, and not hemoconcentration. This was a consistent finding, occurring in all but one case of skeletal trauma and one of hemorrhage.

The picture is what one would expect if there had been, in skeletal trauma and in hemorrhage alike, extensive loss of whole blood at the site of injury, with some subsequent compensatory inflow of fluid into the blood stream from uninjured tissues; and this is apparently the mechanism in these cases.

As is now well known, this is the experience also in battle casualties of the present war, that the loss from the circulating blood volume following traumatic injury is primarily a loss of whole blood rather than plasma.

This evidence therefore indicates that generalized increased capillary permeability with hemoconcentration is not usually a causative factor of the dynamics of circulatory failure in these forms of clinical shock. Noble and Gregersen¹¹ have given this question careful study and have obtained additional data. In cases followed through to recovery after treatment by blood or plasma, Noble has calculated the net change to be expected in the blood volume and compared this value with an actual blood volume determination after recovery. In cases where there was no continued bleeding, two trends have been apparent: first, a dilution of the blood plasma, with the plasma protein concentration falling, by about one gram per cent; and second, in cases followed over several hours, an actual secondary increase in total circulating plasma protein along with a corresponding further inflow of fluid, an average increase of about 10 per cent. This must have come into the blood from the tissues.

These results thus support the views of Blalock⁶ and Phemister⁷ that the loss of blood volume occurs at the site of injury, not into the tissues generally. It is also true, however, that the swelling around an injury consists of serous fluid as well as blood, and one would expect that this local exudation out of the blood may at times exceed the diluting power of the fluid from unimpaired tissues, with resulting hemoconcentration. In some war injuries, such as crushing, this tendency is undoubtedly more pronounced than anything which we have encountered in civilian casualties.

The findings do not rule out the possibility of capillary damage of various kinds in shock; they do show that in these two forms of injury with shock, any effects from such damage did not dominate the active circulation, in the cases which we examined.

"Trapping" of blood in vessels with no active circulation, recently demonstrated in animals in shock,¹² has been found in just one case of our series, a man with gunshot wound of the abdomen and prolonged exposure to cold, with extreme shock. In this case, about 15 per cent of the total blood volume reappeared in the circulation after recovery from shock, in addition to the blood given as treatment.

The next group of traumatic cases, that of abdominal injury with shock, presents some similarities, also some important differences, when compared with shock due to skeletal trauma. As the chart indicates, there were the same basic changes in circulatory dynamics, that is, a

decrease in auricular pressure and in cardiac output. On the other hand, hemoconcentration was a regular finding. The explanation for this is not difficult; all cases had peritonitis with acute serous or sero-purulent exudate in the peritoneal cavity, thus draining large amounts of serous fluid from the blood stream.

A further difference, as compared with shock due to skeletal trauma was the relative maintenance of arterial blood pressure, and the correspondingly higher level of peripheral vascular resistance. Hemoconcentration by increasing blood viscosity, will itself increase peripheral resistance, but is probably not the only factor involved.

The blood volume figures offer what may be an even more significant difference, between the cases of abdominal injury and those of skeletal trauma. Although the plasma volume was diminished the total blood volume showed only a relatively small decrease below the limits of normal, much less than one would expect considering the apparent degree of shock clinically and the actual failure of the circulation as measured by total blood flow.

There is one reservation regarding these data. It has been recognized for some time that when marked hemoconcentration is present the accuracy of the red cell volume determination, using hematocrit and dye technique, is uncertain. The figures obtained appear to be somewhat high. This technical problem is not yet solved. It may be that this accounts in part for the relatively high blood volume recorded in these cases.

If, however, the trend of the observations is correct, one is led into a further interesting field. These abdominal injuries, with peritonitis and infection, were suffering from more than traumatic injury. Clinically they may in this respect approach the medical conditions that one sees, such as pneumonia, malarial fever, or sepsis, with acute failure of the circulation. We have studied a very few of these, and such preliminary data as we have suggest that the circulation fails with normal blood volume, as Stead¹³ also found, indicating some form of vascular or vasomotor collapse. This requires much further study.

This is perhaps a digression but it might be of interest to note that in two cases of acute coronary thrombosis we were able to prove by direct measurement the picture described by Stead,¹³ of decreased cardiac output, low arterial pressure, but normal blood volume, and somewhat increased right auricular pressure. A case of acute pulmonary

embolus gave a similar series of measurements, except that the right auricular pressure, 400 mm. of water, was very high. This latter suggests acute failure of venous return to the left heart only.

The last important category in our series of cases is that of burns. The chart shows the essential features of the dynamics of the circulation, compared with normal findings and with those in other injuries. The picture is qualitatively similar to that in abdominal injury except that the absolute loss of blood volume was larger. There was hemoconcentration due obviously to loss of blood plasma into burned areas; and marked decrease in cardiac output with blood pressure relatively well maintained, and peripheral resistance therefore very high. It is of special interest that the two cases with the highest peripheral resistance had normal hematocrit values, being studied very soon after injury; indicating that the increased resistance was due either to extreme vasoconstriction or to increase in viscosity from causes other than red cell concentration. Auricular pressure was less depressed than in other groups; a factor here was probably the tight pressure bandages that most of these patients had around chest and body, with consequent increase in intrapleural pressure.

It is well known that the initial state of circulatory failure does not usually constitute the chief danger in burns, and it was so in our cases, nearly all showing a favorable immediate response to plasma therapy. There were two patients with overwhelmingly extensive burns who died very shortly after admission, one with pulmonary edema, one of asphyxia following aspiration of vomitus. The difficulties encountered in the complex and protracted later course of burns are outside the scope of this discussion.

Brief mention may be made of severe head injury, eight cases of which were included in our series. While all cases terminated fatally, the picture was not that of shock, but almost the direct opposite, with hypertension, hyperthermia, increased pulmonary ventilation, normal blood volume, and normal or increased cardiac output.

Summarizing these initial measurements made on patients in shock, following various types of injury, one can state that while different injuries led to circulatory failure in different ways, the essential finding in all appeared to be an inadequate venous return of blood to the heart with diminished cardiac output. The anatomical factor immediately responsible in most instances was a deficit in circulating blood volume.

These measurements thus are in confirmation of what might be termed the mechanical concept of shock, which as already related, emerged at the time of the last war and has held a central position since.

Does this, however, provide a full explanation of the dynamics of acute shock? We know something about the blood volume and about the action of the heart. What do we know about the vascular bed, as a whole or in its various parts, and its vasomotor adjustment? On logical grounds it seems reasonable that if we spend so much care measuring the blood volume, we should give some consideration to the vascular envelope which encloses it.

From the relation of pressure to blood flow, as I have already described, one obtains a figure for over-all peripheral resistance throughout the vascular circuit, and this tends to be either maintained or increased in shock, indicating a net or average state of vasoconstriction. It is generally considered that this is a favorable compensatory mechanism, the smaller vascular bed enabling blood pressure and flow to be maintained in spite of smaller blood volume. What regions of the body, however, are shut off from the circulation, in providing this compensatory constriction? How adequate is this compensation, how reliable is it, and what happens if it fails?

The importance of vasomotor failure may be illustrated by the following clinical case:

A young man was brought into the emergency ward suffering from acute alcoholism and a laceration of the scalp which had bled profusely. He was in shock but conscious, and with fairly good pulse volume. An attendant, thinking that a case of head injury should not be allowed to lie flat, sat the patient up. He at once became very pale, pulseless and lost consciousness. He was laid back on the bed, and an attempt made to start an infusion, but before this could be done the patient expired.

Admittedly this patient had lost much blood and was in shock. But the important point is, that without additional blood loss, so slight a thing as momentary change of position precipitated an immediate and fatal circulatory collapse.

The vascular bed is a complex apparatus. Regionally, the vasomotor control of each organ or section of the body can operate independently. The successive channels of flow, arterial, capillary, and venous, also each has its own independent control. The whole is regulated in large

TABLE III

CORRELATION BETWEEN (A) INITIAL BLOOD VOLUME AND INITIAL CARDIAC OUTPUT AND (B) INITIAL BLOOD VOLUME AND INITIAL ARTERIAL BLOOD PRESSURE

Based on measurement in 35 cases of severe skeletal trauma and hemorrhage.

| | <i>Coefficient of correlation</i> | <i>P</i> |
|--|-----------------------------------|------------|
| Total blood volume vs. cardiac output | +0.780 | 0.00000001 |
| Total blood volume vs. mean arterial blood pressure | +0.472 | 0.008 |

part from centers in the central nervous system.

A considerable variety of observations bearing on this question has been made in the course of our work, and I should like to try to assemble these. They may be called the process of vasomotor adjustment in shock, and one may divide the phenomena observed into those which appear to act in a compensatory manner, to maintain the circulation, and those which are apparently phenomena of circulatory or vasomotor decompensation.

First, as to arterial blood pressure. There should be no attempt to minimize the importance of this function. A progressively falling arterial pressure has been considered and will continue to be, one of the dominant manifestations of severe traumatic shock, and clinically one of the most useful because it is so easily measured. Recognizing the importance of this measurement, however, one must also understand its limitations.

Low arterial pressure when present is a good sign of shock, but shock can exist even in advanced degree with an arterial pressure level that is normal or above normal. We have already seen that in certain types of shock, blood pressure tends to be maintained. In Table III, a statistical comparison is made of the relation between initial blood volume in shock and initial cardiac output, on the one hand, and initial blood volume and initial arterial pressure, on the other. The first of these correlations is much better.

Additional information can be obtained about the state of the arterial system, and the blood flow through it, by examining the arterial

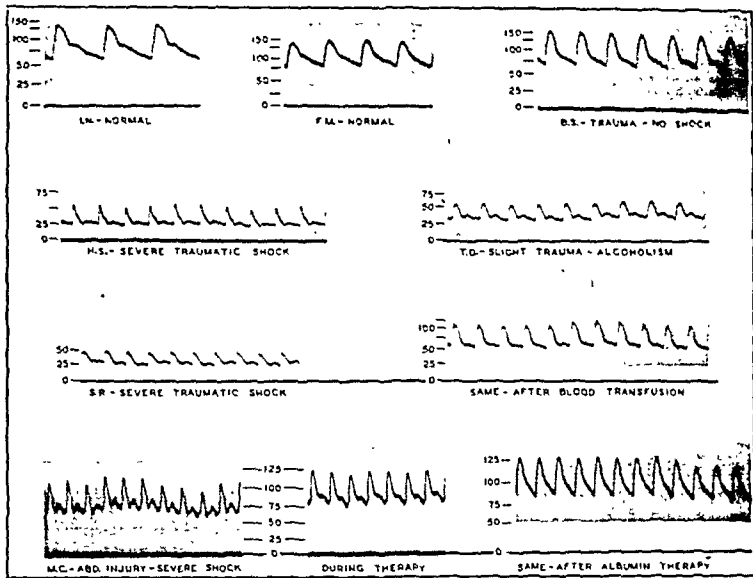


CHART 2. Pressure tracings from femoral artery, using indwelling arterial needle connected with Hamilton manometer.

pressure tracings recorded by the Hamilton manometer, connected with the indwelling needle in the femoral artery. A group of these tracings are shown in Chart 2. At the top are records of normal subjects, with a similar record of an injured patient not in shock, on the right. Below the normal tracings is the record of a patient with severe skeletal trauma and shock. The sharp rise of pressure during systole, and correspondingly rapid collapse in diastole, associated with decreased stroke volume of the heart are well shown. To the right of this is a tracing of an injured patient not in shock, but with acute alcoholism and hypotension. The cardiac output was normal. The pressure curve has a much less collapsing quality than that of the patient in shock.

On the next lower row are tracings of a patient in shock and after recovery; and at the bottom a case of abdominal injury and shock, with low cardiac output but sustained arterial pressure.

Such tracings, when analyzed in conjunction with other findings, give a more exact description of the state of the arterial vascular bed, and flow of blood through it, than is obtainable by other means. Further work on this subject is being carried on by Lauson and Bloomfield.

Granting the condition of average or over-all vasoconstriction in shock, is this phenomenon present to the same degree throughout the body, or is it selective?

In this question, the most accessible parts of the body are of course the skin and superficial tissues of the extremities, and here the evidences of vasoconstriction and reduced circulation in shock are obvious and have long been a part of the description of shock: the pale, cold skin; faint arterial pulse; hemoconcentration of capillary blood. On the venous side, we have found, as have others in the past, that the pressure in the superficial veins of the arm in shock is normal or even slightly high. Since the auricular or central venous pressure is definitely low, this means an increased gradient of pressure along the vein and thus an active venoconstriction.

A selective vasoconstriction in internal organs was suggested many years ago by Gesell² who brought indirect evidence to indicate that the blood flow through the submaxillary gland after blood loss, was reduced to a much greater extent than was the general blood flow.

More substantial evidence on this question can be derived from the renal clearance studies carried out on a number of our patients in shock by Cournand, Bradley and Lauson. Of this very interesting work, defining renal function in the state of shock, I can give at this time only an outline of the aspects that relate the circulation through the kidneys with the general circulation in shock.

The clearance techniques afford, among other things, reasonably accurate measure of total plasma flow, or blood flow, through the kidneys.

Consider that under normal resting conditions, about one quarter of the total blood flow of the body passes through the kidneys, or about one liter of blood per minute.

In shock, while the total blood flow decreases, to, say, half the normal value, the blood flow through the kidneys decreases to one-tenth or one-twentieth, perhaps even less in extreme cases, a mere trickle of a few cc. of blood per minute. This can only mean a powerful vasoconstrictor action of renal arterioles. This is further emphasized in Chart 3, showing how renal blood flow decreases sharply in shock, out of proportion to the fall in mean arterial pressure.

From the point of view of the body as a whole, this blocking of kidney blood flow is for the moment a favorable compensation, providing as it were, a transfusion of several hundred cc. for the more urgent needs of other organs such as brain, heart, and perhaps liver.

So far as concerns the kidneys themselves, with no blood flow

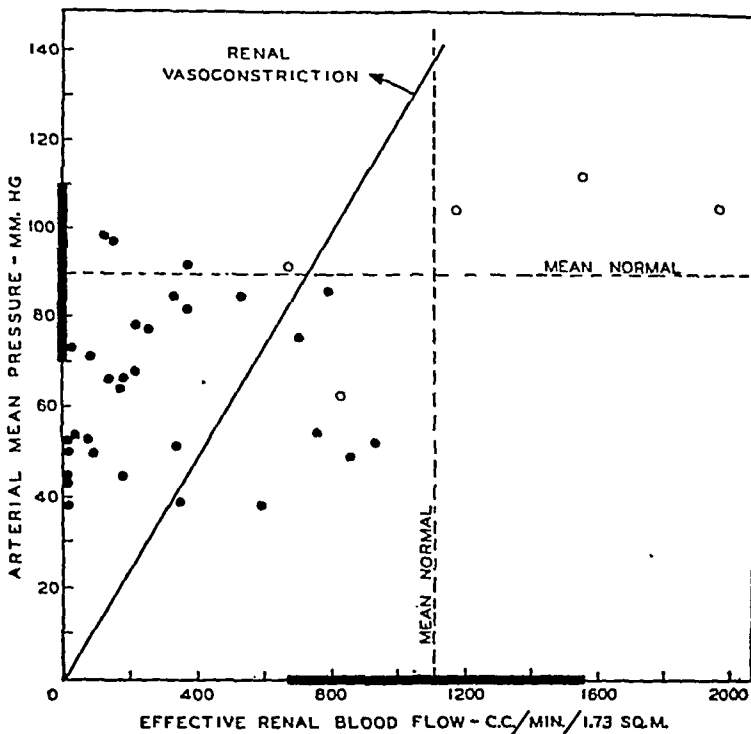


CHART 3. Relation between effective renal blood flow and arterial mean pressure in normal subjects (open circles) and patients in shock (solid circles.).

there is no urine, and in severe shock one finds either anuria or else the secretion of only a very small amount of urine of low specific gravity.

Summarizing this evidence, we have a clear picture of a strongly selective vasoconstrictor mechanism in shock, shutting off almost completely large organ systems or regions of the body not immediately necessary for survival.

We come now to some contrary evidence, indicating that this compensation does not always hold, may fail either gradually or abruptly with unfavorable or disastrous outcome. The case of hemorrhage that I have described was an example of this.

Clinical observation has provided a number of other instances. A patient in severe shock, let us say from hemorrhage or skeletal trauma, will be lying quietly on the bed, when, with no painful or other stimulus, his pupils dilate, he will break out into a sweat, become very pale, pulseless and eventually lose consciousness. If his state of shock is not severe he may recover again spontaneously. Frequently treatment, such

TABLE IV

EFFECT OF POSTURE ON ARTERIAL BLOOD PRESSURE IN SUBJECTS WITH (A) NORMAL BLOOD VOLUME, (B) MODERATE, AND (C) MARKED BLOOD VOLUME LOSS

| Group | Average total blood vol. | No. cases | Position | Arterial blood pressure average | Cardiac output average |
|-----------|--------------------------|-----------|-----------------|---------------------------------|------------------------|
| | cc./sq. m. | | | mm. Hg | lit./min./sq. m. |
| I | 2970 | 7 | Flat Foot-up | 117/74 118/75 | 3.49 3.51 |
| II | 2202 | 6 | Flat Foot-up | 100/62 111/68 | 2.90 3.33 |
| III | 1635 | 4 | Flat Foot-up | 69/42 75/40 | 1.75 1.86 |

as immediate infusion or transfusion, may be needed. Such an episode is not a new observation in shock, but the long period under absolute resting conditions such as has obtained in our work, has provided a good opportunity to study it. The fact of abrupt circulatory failure apparently from vasomotor collapse, seems unmistakable.

The vasomotor balance has been further explored by the simple technique of change of bodily position. This line of inquiry was brought to our research by Duncan, visiting from Johns Hopkins. It consisted in studying arterial blood pressure, and other elements of the circulation, before and during a standard change of body position, this being an elevation of the foot of the bed 12 inches.

Table IV shows the results in a series of cases; so far as arterial blood pressure is concerned, it appears that elevation of the feet produces no change in normal subjects, but a definite increase in patients with moderate loss of blood volume, as if the amount of blood shifted from lower extremities to the central parts of the body improved the vasomotor status. In patients with marked blood volume loss the change was less pronounced, perhaps because there was so little blood left in the lower extremities in these cases.

In a number of instances, auricular pressure and cardiac output were measured in the two positions. These, especially the cardiac output, could not be recorded immediately but required about 10 minutes.

TABLE V

EFFECTS OF A PRESSOR AMINE ("No. 839") ON THE CIRCULATION IN
(A) NORMAL CONTROL SUBJECT (B) CASE OF SEVERE SHOCK
DUE TO SKELETAL TRAUMA, WITH EXTENSIVE BLOOD LOSS

| <i>Subject</i> | <i>Medica- tion</i> | <i>Time after drug</i> | <i>Total blood volume</i> | <i>Art. B.P. mean</i> | <i>Auric- ular pres- sure</i> | <i>Cardiac index</i> | <i>Periph. resist.</i> |
|------------------|-------------------------|--------------------------------|-----------------------------------|-------------------------------|---|-----------------------------|----------------------------|
| Normal | 0 | <i>min.</i> | <i>cc./sq. m.</i> | <i>mm. Hg</i> | <i>mm. H₂O</i> | <i>lit./min. /sq. m</i> | |
| | "No. 839" 20 mg. | 0 | | 131 | + 59 | 4.88 | 1020 |
| Case of shock | 0 | 15 | | 163 | +149 | 2.37 | 4530 |
| | 0 | 0 | 1910 | 34 | — 15 | 1.62 | 1070 |
| | "No. 839" 40 mg. | | | | | | |
| | 0 | 26 | | 45 | — 30 | 1.35 | 1750 |
| | Whole blood, 850 cc. | | | | | | |
| | 0 | 151 | 2170 | 64 | + 16 | 3.44 | 950 |

It is interesting that according to these measurements there was no consistent change either in auricular pressure or cardiac output following foot elevation. It seems probable that the improved vasomotor tone was due to a redistribution of blood flow, a better flow through the brain and less through the lower extremities.

Clinically the foot-up position seemed to be definitely beneficial. Patients were more alert and color improved. In cases with the greatest blood volume losses, this beneficial effect was, however, transitory.

If vasoconstriction is a good thing in shock will more vasoconstriction be better? On theoretical grounds it seemed possible, even though not very likely, that a vasopressor agent might increase the selective vasoconstriction of shock and improve the central blood flow. Table V shows the results of one of the vasopressor amines, similar to paredrinol, when used in a case of severe shock. This drug was kindly provided by DeGraff, Taube, and Herbert of New York University, and these studies were carried out with their coöperation and assistance. As will be seen, there was some increase of blood pressure, but cardiac output was further decreased. Clinically the patient was certainly no better. With subsequent treatment by transfusion, however, he recovered. Thus

TABLE VI

INFLUENCE OF ALCOHOLISM UPON VARIOUS HEMODYNAMIC MEASUREMENTS IN 30 SUBJECTS WITH SEVERE SKELETAL TRAUMA AND HEMORRHAGE

| | No. of cases | Total blood volume average | Mean arterial pressure average | Cardiac output average | Stroke volume average | Peripheral resistance average |
|------------------------------|--------------|----------------------------|--------------------------------|-----------------------------|-----------------------|---------------------------------|
| | | cc./Sq. M./ B.S. | mm. Hg | lit./min. Sq. M. B.S. | cc./beat | Dynes cm. ⁻⁵ Sec. |
| Group I. No oligemia | | | | | | |
| a) No alcoholism | 2 | 3250 | 101 | 3.88 | 85 | 1150 |
| b) Mild alcoholism | 3 | 2660 | 94 | 3.62 | 71 | 1245 |
| c) Severe alcoholism | 2 | 2895 | 50 | 3.11 | 59 | 738 |
| Group II. Moderate oligemia | | | | | | |
| a) No alcoholism | 4 | 2125 | 79 | 2.87 | 60 | 1371 |
| b) Mild alcoholism | 3 | 2407 | 46 | 2.52 | 45 | 820 |
| c) Severe alcoholism | 0 | .. | .. | .. | .. | .. |
| Group III. Marked oligemia | | | | | | |
| a) No alcoholism | 11 | 1720 | 51 | 2.02 | 29 | 1336 |
| b) Mild alcoholism | 3 | 1680 | 47 | 1.48 | 24 | 1536 |
| c) Severe alcoholism | 2 | 1685 | 33 | 1.51 | 22 | 1053 |

this attempt to better the vasomotor compensation already present in this particular type of shock due to marked blood loss, was a failure. One cannot extend this conclusion, however, to all types of shock. The use of drugs in the various forms of shock deserves much further study.

British investigators distinguish between the excessive vasoconstrictor response, such as that just described, and the so-called vaso-vagal reaction, with falling blood pressure and slow pulse, essentially that of syncope.

McMichael¹⁴ has very recently published some interesting results bearing on this problem. Using the method of right heart catheterization, he and his collaborators studied in normal subjects the effects of a large phlebotomy carried to the point where the subject fainted. They found that cardiac output decreased during the phlebotomy, but when syncope occurred there was no further drop in cardiac output although the arterial blood pressure decreased by one-half. Pulse was markedly slowed. By the use of a plethysmograph on the arm they obtained evidence of increased muscle blood flow. The state of syncope was relieved promptly following administration of methedrine. These ex-

cellent experiments thus give impressive evidence of the importance of vasomotor control in shock and shock-like states.

Of interest in this field also are the studies by Cournand on the effects of acute alcoholism upon the state of shock. There is no lack of such material in the admitting service at Bellevue Hospital; nearly half of our cases of acute shock have had, to a greater or less degree, acute alcoholism at the time of admission. The whole clinical and physiological picture of shock was in fact quite confusing until Cournand added blood alcohol determination as a routine measurement in all cases.

Table VI shows the effects of alcohol as a vasodilator agent, reducing the mean blood pressure both in the normal group and in those with loss of blood volume. With extreme blood loss and severe shock, the drop in blood pressure was less in absolute terms, but cardiac output showed a further fall in the alcoholic cases.

The effect tended to persist even with replacement therapy by blood or plasma. While cardiac output increased, blood pressure remained low.

Clinically as well as physiologically, the effects of alcoholism superimposed upon those of shock were most unfavorable. The individual was in a very precarious state and sudden exitus, usually with a convulsive seizure of some sort, occurred more than once.

Fat embolism has frequently been reported as a cause of acute circulatory failure in shock. This condition was not demonstrated in any of our autopsied cases.

These observations on the vascular bed in shock may be summarized briefly as follows:

1. In shock with blood loss there is a tendency to selective vasoconstriction, which is compensatory.
2. This compensation may fail, either gradually or suddenly. The patient in shock is in an unstable state, and the smallest additional trauma or physical disturbance may have profound and disastrous effects.
3. Elevation of the feet in shock usually raises arterial blood pressure, and is beneficial clinically.
4. Drug therapy of shock is not very satisfactory at present but certain drug effects may prove to be helpful, for treatment of particular conditions of peripheral circulatory failure.
5. Alcohol causes marked vasodilatation which is clinically unfavorable.

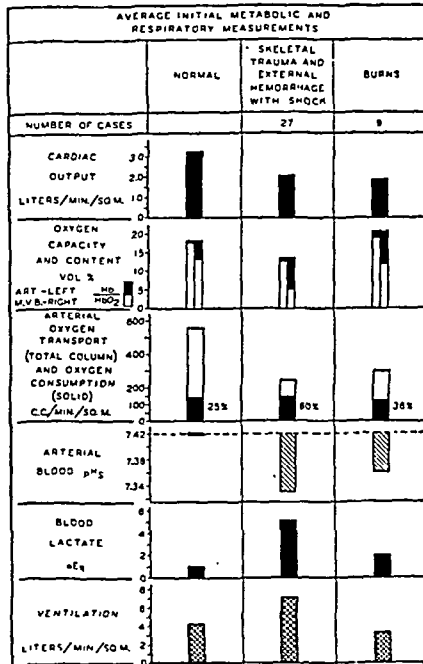


CHART 4. For further explanation see text.

6. The most effective treatment is replacement of blood volume. This will be considered presently.

Given the type of circulatory failure which I have described, what are the consequences of this upon tissue respiration and metabolism? Chart 4 shows, for normal subjects, for a combined group of skeletal trauma and hemorrhage, and for a group of burn cases, some of these measurements.

The first row gives cardiac output, providing an index of the state of the general circulation.

The second row consists of sets of double columns, the left one representing arterial blood, the right venous blood. The upper or black segment of each column gives the amount of reduced hemoglobin present, the lower white segment, the amount of oxygenated hemoglobin. Thus this set of double columns indicates presence or absence of anemia, and level of oxygen saturation in both arterial and venous blood.

The third row presents in graphic form an interesting relationship. This was worked out by Lauson, to whom I am indebted not only for this but for all the illustrative charts.

The solid blocks below indicate oxygen consumption in cc. per

minute. The height of the unshaded blocks above gives the arterial oxygen transport, or total oxygen brought to the tissues by the arterial blood. This value is simply the cardiac output multiplied by the oxygen content of the arterial blood.

To take first the cases of skeletal trauma and hemorrhage with shock, one finds that the drop in cardiac output together with the anemia brought necessarily a very low oxygen in the venous blood, thus indicating also anoxia of tissues, one of the primary phenomena of the state of shock. The arterial oxygen saturation was, however, normal.

As shown in the chart, the normal subjects in their tissue oxygen consumption used only 25 per cent of the total oxygen conveyed by the blood, leaving a reserve of 75 per cent; whereas in the shock cases, 60 per cent of total available oxygen was consumed. It will be noted that the average oxygen consumption in this group was not decreased, as compared with the average normal value. The normal subjects were, however, under basal conditions, while the cases of injury were not. Some of the latter were also quite restless. Oxygen consumption in those patients in shock who remained physically at rest was diminished below normal values.

Arterial pH was low, an uncompensated acidosis, associated of course with decreased CO_2 . That this was in large part due to increase in fixed acids, products of incomplete oxidation, is shown by the high values for blood lactate. The degree of acidosis varies greatly, the pH ranging from values almost within normal limits, to 7.20 or less. The lowest were in two cases of exposure to cold, with pH levels just under 7.00.

Pulmonary ventilation was on the average, increased; it was correlated, though not very closely, with the extent of acidosis.

In burns, representing forms of shock with hemoconcentration, this condition brought significant differences in the state of metabolism. Although the cardiac output was low, the amount of oxygen in the venous blood was considerably greater than in trauma or hemorrhage, and the total oxygen transport was also greater. This suggests that tissue anoxia was less, and this is borne out by a lesser degree of acidosis and a smaller blood lactate.

A special feature, however, of the cases of burns was the frequency with which arterial oxygen unsaturation occurred without pneumonia or recognizable pulmonary pathology. This has now been found in

TABLE VII

SERUM ELECTROLYTES, RANGE OF VALUES IN 4 CASES OF SEVERE SHOCK, DUE TO HEMORRHAGE (2), SKELETAL TRAUMA (1), GUNSHOT WOUND AND EXPOSURE TO COLD (1)

| <i>Cations</i> | <i>Range, Milli-Eq.</i> | <i>Anions</i> | <i>Range, Milli-Eq.</i> |
|----------------------|-----------------------------|------------------------------|-----------------------------|
| Sodium | 139.8 to 145.8 | Bicarbonate | 6.0 to 15.0 |
| Potassium | 3.4 to 5.5 | Chloride | 106.0 to 115.5 |
| Calcium | 4.0 to 4.2 | Phosphate (inorg.) | 1.9 to 5.1 |
| Magnesium | 1.7 to 3.4 | Albumin | 6.5 to 11.4 |
| | | Globulin | 2.1 to 3.4 |
| Total base | 150.1 to 158.7 | Lactate | 2.7 to 14.5 |
| | | Total acid | 141.3 to 151.0 |

Arterial pHs range, 7.24 to 7.09.

Total base minus total acid, 8.0 to 11.8 Milli-Eq.

twelve of nineteen cases and varied in the range from 81 to 88 per cent. Inhalation of hot or irritant gases was probably a factor in most cases, though not in all. The condition persisted from 3 to 7 days after injury.

There were a number of types of injury in the whole series, other than the four groups just described. Of these, the chest injuries were perhaps the most important. These can be of course most complex and it is difficult to make general statements about them. Arterial oxygen unsaturation was found in all of our cases. An interesting phenomenon was that oxygen unsaturation became more marked after recovery from shock, following transfusion, as if there were a tendency to pulmonary congestion aggravated by increase in blood volume.

In a small series of four cases, the electrolytes of the blood plasma were measured in the state of shock (Table VII). No significant deviations from normal were found in the values for total base, potassium, sodium, or calcium. Of the anions, bicarbonate was of course decreased, chloride somewhat increased, phosphate unchanged, lactate increased. Total base was considerably higher than total acid—even with lactate included in the latter—from 8 to 11 millimols. Evidently other fixed acids were present.

The question of failure of the heart itself in acute traumatic shock has been raised by many investigators in the past. We have not ob-

tained any satisfactory evidence on this question, from our observations; except that with replacement of blood volume by transfusion, the heart responded by increased cardiac output in every instance except one; and in no case did the auricular pressure increase to abnormally high (congestive) levels. In subsequent days, following recovery from acute shock, a number of cases did develop evidence suggestive of cardiac insufficiency. The clinical situations here were complex, and are beyond the scope of the present discussion.

There remains to be considered the manner in which the circulation is restored following adequate treatment of shock, or fails if treatment is unsuccessful.

It has long been recognized that treatment for shock must be begun at the earliest possible moment, and all the experience that we have had justifies this principle. The severity of injury and the duration of shock are the critical factors in prognosis.

Just what the elements are that cause progressive deterioration as shock continues—those which have been called the sustaining factors in shock—is not known. Much important experimental work is in progress in this field; but it is difficult to make controlled observations in clinical cases. We have a few data which may be relevant.

As deep shock continued in our cases, in the absence of added trauma, and apparent absence of further blood loss, there was usually not much further change in blood volume. Cardiac output and arterial blood pressure tended to fall to lower levels. The state of acidosis increased steadily and blood lactate also progressively increased. Thus the effects of anoxia accumulated.

As a matter of fact, when examined within the first two or three hours after injury, in skeletal trauma or hemorrhage, the arterial pH was but little reduced, sometimes within normal limits. Acidosis was thus obviously not an early manifestation of shock but developed with continuing circulatory failure.

The response to treatment also depended upon the duration of shock. The one case in which the cardiac output did not increase appreciably when the blood volume was restored to normal was a woman who had had a massive gastrointestinal hemorrhage nineteen hours before. In a number of other instances, while the cardiac output and arterial pressure improved considerably following transfusion, death occurred very shortly from respiratory failure, sometimes preceded by

a slight convulsion.

Although the brain appeared to be the first organ to fail with progressive anoxia, there was evidence, on subsequent days, of damage to other systems, coming on some time after the acute shock had been overcome. Pulmonary edema was a frequent and difficult complication during the first week. Whether this was on the basis of pulmonary or cardiac damage we have not been able to determine.

One patient who suffered a traumatic rupture of the jejunum and was in deep shock for many hours, developed an acute renal insufficiency, with nitrogen retention and minimal urine output of low specific gravity. This case, unique in our series, is similar to the crush syndrome studied by Bywaters¹⁵ and others, and recently reproduced in animals by Phillips and Van Slyke¹⁶ by shutting off the renal circulation for several hours.

These clinical examples have been perhaps somewhat unrelated, but one cannot emphasize too much the many and disastrous effects of long continued shock.

The basis of the effective treatment of acute shock has been, ever since the last war, the replenishment of the actively circulating blood volume. The therapeutic agents commonly used are of three types: (1) saline or other crystalloid solutions; (2) plasma and the various plasma substitutes; and (3) whole blood.

There has been a tendency recently to dismiss intravenous saline infusion as of little value. We have not many observations on this point, but measurements in a few cases of shock before and after a large rapid intravenous saline infusion of 1500 to 2000 cc. showed that while the blood volume, measured from one to three hours after the infusion, was increased by only two or three hundred cc., the cardiac output was increased considerably, often restored to normal. We have no figures on the total duration of this effect. Clinically it did not appear to be long sustained. As a temporary measure, intravenous saline if given rapidly still holds a definite place in treatment.

The vast amount of practical experience proving the value of whole plasma, dried plasma, and plasma proteins in shock requires no comment here. In confirmation of much other work, we have found that in the absence of further blood or plasma loss, most of the protein administered by such transfusions still remained in the circulation at the end of six hours, with corresponding increase in plasma volume,

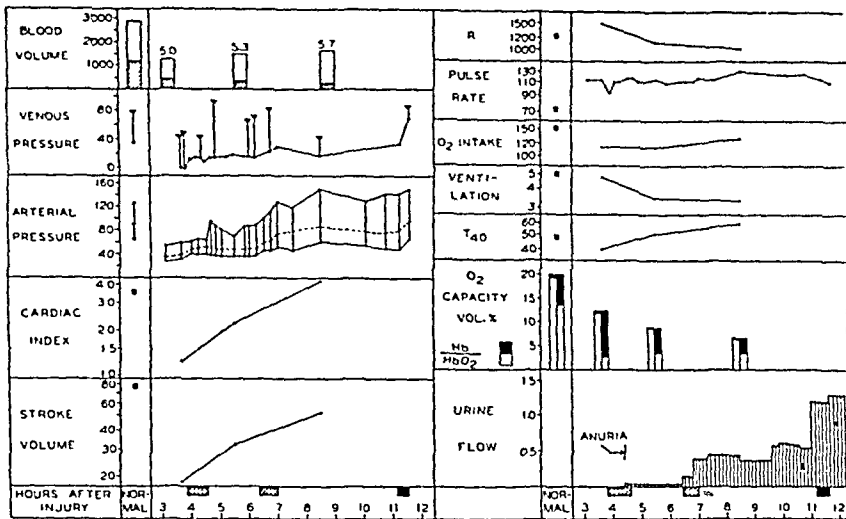


CHART 5. Patient H.S. Course during treatment and recovery from shock. Figures above blood volume blocks refer to plasma protein concentrations. In "Venous Pressure" column, triangles refer to peripheral venous pressures, dots to auricular pressures. "T40" is blood CO_2 content at 40 mm. CO_2 pressure. In "O₂ Capacity" column, left hand block in each group refers to arterial blood, right hand block mixed venous blood. Cross-hatched blocks at bottom indicate times of albumin therapy, solid block whole blood transfusion.

and recovery from shock.

It is worth pointing out, however, that when whole blood has been lost in large amounts, as in hemorrhage or skeletal trauma, replacement by plasma alone will produce an acute anemia and this may actually limit the quantity of plasma that can be safely used. A case record will illustrate this point:

H.S., a 48-year-old white female, jumped from a third story window and suffered fractures of both os calci, both ankles, pelvis, and transverse processes of several vertebrae. The patient was conscious but depressed, complained of thirst, was pale, perspiring about the head. Extremities were cold, lips and ears cyanosed. The first set of measurements (Chart 5), carried out three and one-half hours after injury, are shown on the chart. With a 50 per cent loss of blood volume, hematocrit of 32, complete anuria, cardiac output only 1.24 liters per square meter of body surface, the state of shock was obviously severe. The cross-hatched blocks at the bottom of the chart indicate therapy in the form of 5 grams of albumin solution, equivalent to 1000 cc. of whole plasma. As seen in the chart, this brought some increase in plasma volume, blood pressure and cardiac output. Red cell volume

decreased further, probably from further bleeding. Urine flow began but was minimal. A second 50 grams of albumin, given between the sixth and seventh hours after injury, was followed by a marked dynamic response. Though blood volume was still low, and hematocrit down to 16 there was an increase in cardiac output to or even above normal, and corresponding rise in arterial pressure. Pulse rate remained high, peripheral resistance diminished. The significant point here is that while total blood flow was restored, total oxygen transport to the tissues was still much below normal, on account of the severe anemia.

The patient was improved but still very pale. A 500-cc. whole blood transfusion was given before she was transferred to the operating room, and her subsequent course was satisfactory.

The preference for whole blood in treating these types of injury has been increasingly emphasized in reports of military casualties in this war. Whole blood is needed, and in substantial amounts. The average blood volume loss in severe shock in our cases was nearly two liters. While there was often a striking temporary response of the circulation to a few hundred cc. of blood, sustained recovery required at least 1000 cc. to 1500 cc. Failure to respond to this, or recurrence of shock after improvement, especially if treatment had been given early, usually indicated continued bleeding.

An example of a case, similar to the preceding, of severe skeletal trauma will demonstrate the process of recovery from shock, following whole blood transfusion:

M.M., (also) a 48-year-old female, (also) jumped from a third story window, sustaining fractures of the sacrum, pelvis, transverse processes of all lumbar vertebrae, and one rib. When seen three and one-half hours after injury she complained of pain and thirst, was mentally depressed, pale, with cold extremities. Chart 6 shows the measurements made during six hours of observation. At the start, the decreased blood volume, low auricular pressure, low arterial and pulse pressures, decreased cardiac output and stroke volume, demonstrated severe shock. Of the measurements on the right side of the chart, particular mention may be made of the low renal plasma flow and filtration rate. The arterial pH value, 7.37, was practically normal, this being early in shock. Blood lactate was 31 mg. per 100 cc.

At the times of the two arrows at the bottom of the chart, two large doses of adrenal cortical extract were given, without demonstrable

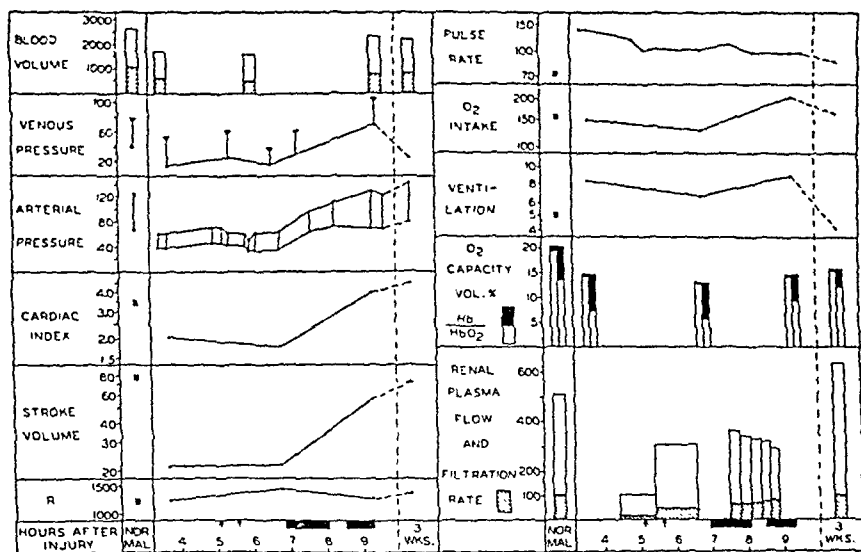


CHART 6. Patient M.M. Course during treatment and recovery from shock. For explanation of symbols see Chart 5.

effect. Restudy at the seventh hour after injury showed the circulation about the same. Arterial pH had decreased to 7.30, blood lactate had increased slightly.

The solid blocks at the bottom of the chart indicate two transfusions, 1155 cc. of whole blood in all. The response of all aspects of the circulation is striking. Contrasted with the results of therapy in the previous case are the high level of venous oxygen, the increased tissue oxygen consumption, and the slowing of the pulse rate. It is interesting that with recovery of the circulation the arterial pH moved from 7.30 to the normal value of 7.42.

Three weeks after injury there was still a moderate anemia, and slight decrease of blood volume.

Table VIII gives a summary of comparative results in shock due to skeletal trauma and hemorrhage with the use of saline, plasma (in this case albumin solution), and whole blood. The point that I should like to make is that with essentially the same amounts of fluid retained in the circulating blood, the plasma-treated cases had a larger increase in cardiac output than those treated with whole blood, and yet, because of anemia, no greater increase in total oxygen transport to the tissues.

Restoration of blood volume brings the patient out of acute circulatory failure but is not complete treatment in itself. Injured tissue means local edema, particularly extensive in burns; and Rosenthal's recent

TABLE VIII
COMPARISON OF EFFECTS OF WHOLE BLOOD,
BLOOD SUBSTITUTE (CONCENTRATED HUMAN ALBUMIN)
AND SALINE IN SKELETAL INJURY AND HEMORRHAGE WITH SHOCK

| Type of therapy given | Fluid equiv. | No. of cases | | Average total blood volume | | Average hemat. | Average cardiac output | | Total arterial oxygen transport | |
|---------------------------------------|--------------|--------------|---------|----------------------------|----------|----------------|------------------------|----------|---------------------------------|----------|
| | | | | cc./sq. m. | % change | | lit./min. /sq. m. | % change | cc./min. /sq. m. | % change |
| Whole blood, 712 cc. | cc. 712 | 11 | Initial | 1734 | | 31 | 1.76 | | 201 | |
| | | | Final | 2261 | +31 | 33 | 2.88 | +64 | 356 | +77 |
| Concentrated human albumin, 42 gms. | 840 | 6 | Initial | 1863 | | 36 | 2.27 | | 298 | |
| | | | Final | 2207 | +18 | 26 | 4.15 | +83 | 425 | +43 |
| Intravenous saline infusion, 1644 cc. | 1644 | 6 | Initial | 2070 | | 37 | 2.81 | | 379 | |
| | | | Final | 2234 | + 8 | 32 | 3.94 | +40 | 487 | +29 |

experiments¹⁷ indicate a need for increased amounts of sodium salts to provide for this necessary temporary increase in extracellular fluid. The latter has also been losing fluid into the blood stream to provide for hemodilution. The clinical work of Lyons¹⁸ points equally strongly to the necessity for maintenance of protein intake in injured subjects. Fluids, salts, and food should be started by mouth in the post-shock state as soon as tolerated.

The status of oxygen therapy is not yet fully defined although there has been much investigation of this subject over many years. It is frequently a necessity in chest injuries; and, from our data, might well be helpful in many cases of burns. The fact that the arterial oxygen saturation is normal in other types of shock does not rule out a possible effect of oxygen therapy, since a small increment of oxygen can be carried by arterial blood, especially if high concentrations of oxygen are inhaled. Animal studies on this question are somewhat controversial. Further investigation in clinical cases should be carried out.

On the question whether the body should be warmed or cooled during shock, it will have been apparent from our results that the central circulation is better maintained if the volume of blood in the extremities is minimal, and in this sense, as suggested by the work of Blalock,¹⁹ cool extremities, particularly the avoidance of external heat applied to them, should be beneficial. This does not mean that the body as a whole should be subjected to cold. It has long been known that exposure to cold affects shock most unfavorably; two of our cases of most profound shock, for example, both of them fatal, were caused by prolonged exposure to cold.

This presentation has been limited in scope, concerned primarily with the mechanism of acute traumatic shock in man, and depending largely upon material from one clinical investigation. It has been possible to mention only a few of the many excellent recent investigations, both experimental and clinical in this field.

Acute progressive or secondary shock, as seen in clinical cases following injury, is a failure of the circulation presenting in its fully established state a consistent physiological pattern. The basic dynamic feature, failure of return of blood to the heart, with diminished blood flow and tissue anoxia, long recognized from experimental evidence, can be said to have been proved also in human cases of shock. There are a number of ways in which shock can develop, from different types

of injury, with the causative factors acting in varying degrees. The loss of circulating blood volume and the behavior of the vascular bed are both of primary importance.

Shock must also be considered as the first stage of a profound bodily disturbance whose consequences continue and may progress for a long time. From the beginning, the management of the case should be planned so as to treat not only the acute circulatory failure that exists, but also the long period of illness and bodily depletion that may follow.

As to the subject itself there is a very great deal still to be learned: the further study of types of shock without trauma or blood loss; the possibilities of drug therapy; the question of toxic factors, if present, and how to identify and neutralize them; and most of all, the problem of passing from the stage of acute shock to that of maintenance, nutrition and the combatting of anemia and infection. The greatest mistake is to suggest, as some have done, that shock is a problem that has been solved.

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INTERNATIONAL HEALTH*

The Hermann M. Biggs Memorial Lecture

WILBUR A. SAWYER

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IT WAS many years ago, while I was Executive Officer of the California State Board of Health, that I had occasion to consult Dr. Hermann M. Biggs in his New York office regarding the problem of the interstate migration of the tuberculous. The memory of the substance of our talk is now dim, but I brought away a lasting impression of the quiet thoughtfulness and sincerity of that pioneer and statesman in public health. To give one of the Hermann M. Biggs Memorial Lectures is a privilege which is deeply appreciated. That my subject is one which was of great interest to him is shown by the program and principles which he advocated for the League of Red Cross Societies after the first World War. We need desperately similar statesmanship so that this second global catastrophe will be followed by an adequate measure of health coöperation among nations.

What will be done on the international level to protect and promote health after this war? The opportunities will depend in large part on momentous decisions in the political field, and any plan would be on the assumption of a period of peace and security. The same problems were faced after the last World War when the Health Organisation of the League of Nations was created to guide and assist international coöperation in health. Its achievements were notable and the setback which came with the collapse of the League was through no fault of its own. The fundamentals of a future health organization will probably be determined by the overall world organization to be brought into being by our statesmen. The question may be raised in their deliberations why health matters should be included among those of prime international concern. It may even be suggested that, except for the administration of international conventions, the protection of health be left exclusively to the individual countries. On what experience and

* Read April 6, 1944 at the Stated Meeting of The New York Academy of Medicine.

evidence do we base our conviction that an official international health organization with a broad field of interest is desirable and even essential if man is to enjoy a reasonable measure of physical welfare along with the hoped-for enduring peace?

EARLY INTERNATIONAL HEALTH ORGANIZATION

The oldest and most generally accepted international health function is the regulation of quarantine. When it became realized that plague, cholera, and yellow fever could be carried by ships, it was natural that frightened countries should take drastic measures to protect themselves through quarantine. Ships were detained and merchandise destroyed, with every country acting for itself. Inevitably such individual and sometimes capricious and excessive action led to a demand for regulation through international agreement. Beginning in 1851 a series of international conferences was held in Europe and produced understandings with regard to maritime quarantine, and in 1892 the first "sanitary convention" was produced. More meetings followed and in 1902 there were established for the American republics the Pan-American Sanitary Conferences. In the hope of achieving world-wide agreement in matters of quarantine, the International Public Health Office was authorized at a convention in Rome in 1907 and soon afterward was provided with headquarters in Paris. It has since then been the principal agency for framing international conventions in health, bringing them before the interested nations for adoption, and taking care of their administration. To act wisely in planning agreements it has been necessary for the Office to weigh a wide range of experience and observations at its meetings, for the situation is ever changing. Over a decade ago the rapid expansion of travel by air brought urgent problems to which the rules for maritime quarantine were not applicable. Air routes were being planned between the known endemic areas of yellow fever in Africa and highly vulnerable countries like India. So the Office after due deliberation prepared a Sanitary Convention for Aerial Navigation which has helped solve the knotty problem of limiting the spread of yellow fever and other diseases by airplane.

After the first World War the need for an international health agency with wider scope was recognized. Administration of quarantine measures to prevent the spread of certain pestilential diseases between countries was no longer considered sufficient, so in 1923 the Health

Organisation of the League of Nations came into being in Geneva with a greater range of activities. The advantages of the absorption of the International Public Health Office by this new agency were carefully weighed, but merging the two was impossible, for the assent of the governments which had set up the Office could not be obtained. The two organizations therefore functioned separately, but with a system of liaison which lessened the disadvantages. Both organizations are now almost at a standstill because of the war, and it should be an opportune time, when the general plans for world health organization are again formulated, to consider just how the world health agency had best be set up and with what range of activity. The separate functioning of the two agencies—the International Public Health Office, with its interest limited to the prevention of the spread of major communicable diseases, and the Health Organisation of the League—had one advantage. It brought out clearly that there were many important new functions for an international health organization and that quarantine would be only a minor part of the ideal program.

The organization which I have served for the past quarter century is a non-official agency for international public health work, and its experiences as a pioneer in this field illustrate several of the points which I wish to make. The International Health Commission of The Rockefeller Foundation was established in 1913 and renamed the International Health Board in 1916 and the International Health Division in 1927. It is a private agency, but its world-wide activities, like those of the official international health organizations, are carried on with and through governments and at their invitation. Its health work is largely on the frontiers of public health knowledge where it explores a few selected fields with a large measure of freedom for the purpose of helping governmental health departments to become more effective. When useful new knowledge and experience in its application have been acquired, the Division withdraws, leaving it to the official health authorities to follow up the gains. To strengthen the coöperative programs and increase their prospect of permanency, the Division trains professional staff for the governments through fellowships and frequently gives travel grants so that officials can compare their own health work with that of other countries. These activities and the policies followed had their counterpart in the program of the Health Organisation of the League of Nations. In fact, in the early years of that agency,

The Rockefeller Foundation contributed financially toward items of its program, realizing that the new organization and the International Health Division had many common objectives.

QUARANTINE

Quarantine still plays an important role in international health, though a much changed one. Ships are seldom held up for any great length of time, and radio pratique enables many vessels to reach their docks without noticeable delay. The quarters for passengers at quarantine stations are largely empty. Immigrants are examined as far as possible before they sail. Steps are taken to keep ships rat-free. More attention is being given to the control of dangerous disease in the exporting countries where it is prevalent, and to making the receiving countries as nearly non-infectible as possible.

Malaria offers an example of an important disease to which the ordinary type of quarantine can hardly be applied. Malaria is widespread in most tropical and subtropical regions and present in the United States. We hear it called the "number one disease" in the present war. Infected travelers or soldiers returning to this country after visiting malarious regions may apparently be well after an attack but may nevertheless come down later with a relapse, infecting local anopheline mosquitoes and starting new outbreaks. Quarantine at the borders would be of little avail. Reliance must be placed chiefly on recognizing the relapses so that prompt treatment will be given and on making the community non-infectible by intensifying mosquito control where dangerous anophelines are present.

There is a phase of malaria control, however, which requires the vigilance of quarantine officers and also serious international coöperation. Some anopheline mosquitoes are much more effective in transmitting malaria than others. Certain islands of the Pacific are free from anophelines while others are swarming with dangerous species. The transfer of effective anopheline vectors from continent to continent or between islands by airplanes must be controlled. This is now being done on an increasing scale by spraying planes with efficient insecticides at airports and during flight. Needless to say, this requires a high degree of international coöperation.

A recent episode illustrates the need for constant vigilance to prevent the transfer of dangerous anopheline mosquitoes even between

continents. *Anopheles gambiae* is an extremely efficient transmitter of malaria. It is widespread in Africa, but fortunately it has been completely absent from the Western Hemisphere except for its recent brief sojourn there. In March of 1930 Mr. R. C. Shannon, an entomologist of the International Health Division attached to the yellow fever laboratory in Bahia, Brazil, while collecting specimens one Sunday, as biologists will do, discovered *gambiae* larvae in shallow water on the outskirts of Natal. Subsequent events indicated that this mosquito must have been recently introduced, probably from Dakar by fast ship. In the following rainy season there was an outbreak of malaria of unprecedented severity in the vicinity of the breeding places discovered, showing that the mosquito had already become well established. For a few years the mosquito spread rather slowly, but later it occupied large valleys to the west, reaching places 300 miles from its starting point. Each major advance was accompanied by extreme epidemics of malaria with numerous deaths. By 1939 the situation was grave and it was realized that the tropics and subtropics of the whole continent were threatened. The Government of Brazil and the International Health Division decided to coöperate in a determined drive to eradicate *Anopheles gambiae* from South America. Dr. F. L. Soper of the Division's staff was put in general charge. Adequate funds were made available and at the height of the campaign over 4,000 men were employed. Fantastic as the undertaking appeared to most malaria authorities at the beginning, the mosquito was completely eradicated within two years, and now, with the control measures stopped, the immediate problem is one of quarantine to prevent its reintroduction. The chief reliance is on enforcement of the adequate disinsecting of planes coming to Brazil. With the rapid rise in military and civilian air travel the danger of bringing *gambiae* back has increased and the quarantine measures have had to be intensified. On a number of recent occasions *gambiae* mosquitoes were found on arriving planes and once even on land at Natal, showing that maximum precautions are essential. As a further safeguard there is urgent need for organizing more adequate *gambiae* control at African airports and in adjoining civilian communities. The whole problem of spreading dangerous insects by airplane offers a fine opportunity for successful international collaboration now that such effective methods are available.

Extreme precautions must sometimes be taken to prevent infected

insects from bringing in the germ of an exotic disease, to be spread by insects already present. Such occurrence would be just the reverse of what happened in the gambian episode, in which a foreign insect came in, greatly to multiply a local disease. The vector of yellow fever in urban epidemics is *Aedes aegypti*, the "stegomyia" of history. Once infected by biting a sick person, the mosquito carries the virus and remains infective for life. The danger from the introduction of such mosquitoes seems even greater than that from bringing in infected persons, particularly as travelers and airplane crews visiting endemic areas are now usually immunized by vaccination. The necessary international coöperation by quarantine services in the case of yellow fever consists in the strict observance of the Sanitary Convention for Aerial Navigation, the systematic disinsecting of airplanes which have touched in endemic areas, and the inspection of passengers from such places with surveillance during the incubation period when indicated. International coöperation should go further than this. Urban yellow fever should be completely eliminated by locally exterminating *Aedes aegypti*, and jungle yellow fever should be limited and kept from reaching cities and arteries of travel by systematic vaccination of the populations which are critically situated. Mass vaccination for this purpose is now being done in certain countries in Africa and South America. The potential receiving countries on their part should make their own danger areas aegypti-free. It goes without saying that such a diverse and widespread system of control, adequate as it seems to be when completely applied, requires the supervision of an alert international health organization. Otherwise the very successes will lead to a period of overconfidence and to relaxation of precautions, and one country will not be aware of storms brewing in another.

CREATION OF NEEDED KNOWLEDGE

Medical and public health discoveries are as a rule rapidly and widely proclaimed through scientific journals in accord with the established tradition that the whole world is entitled to the benefits of such information. Independent scientific publication and international professional meetings should continue under conditions of maximum freedom. Nevertheless, both the production of public health knowledge and its distribution can be greatly facilitated and augmented by suitable international organization and assistance.

It is not infrequently said by those who view the endless parade of scientific publications and announcements, that we know almost enough and that the urgent need is for organization to apply existing knowledge. One who goes into the field to do the applying, however, is quickly disillusioned. He finds that the unknown is vastly greater than the known, and soon his road ends at the chasm of a missing essential fact. One such difficulty was faced and overcome, for example, when Walter Reed and his associates, spurred on by a pressing need in Cuba, determined definitely that yellow fever is transmitted by a mosquito. Given this knowledge, sanitarians could immediately transform desperate and futile efforts of control into most effective ones.

It is the scientific worker in the field and the official responsible for disease prevention who see most clearly what the crucial missing facts are. Likewise the health workers in the international field have the best view of the needs of the world as a whole. In addition to the fundamental investigations in our well-equipped institutions of teaching and research, there must always be field research and related laboratory studies focussed sharply on a recognized immediate need. The research, though thus directed to a practical end, can nevertheless be kept on the highest scientific level if suitably organized and adequately supported. It will be most fruitful if carried on, with international direction and assistance, in the countries offering the best opportunities for the study of the diseases in question in their natural environment. Research is necessary in the depths of the jungle and in country villages, as well as in the laboratories of our large cities.

The advantages of an international approach to the study of the nature and epidemiology of an important disease are illustrated by the work of the staff of the International Health Division on yellow fever during the past two decades. In 1925 there was very little recognized yellow fever in northeastern Brazil, where the Division had been carrying on control operations. So it was decided to set up another project under Dr. Henry Beeuwkes in West Africa, where the disease was reported to be present. For two years the results of the studies on etiology were distressingly negative, but in 1927 the fundamental discovery that the rhesus monkey is susceptible to yellow fever and can be used satisfactorily as a laboratory animal was made by Stokes, Bauer, and Hudson. This made a rapid advance possible without human experimentation. Immediately a series of observations was undertaken

which removed all doubt as to the nature of the causative virus and confirmed the observation of the Reed Commission that it is filterable. The investigators established also the principal characteristics of the experimental disease and studied its transmission by the mosquito *Aedes aegypti*.

The question was raised soon afterward whether the disease in Africa was the same as the one in South America and whether the African observations were applicable there. Therefore it was decided by the Division to open a yellow fever laboratory in New York at the Rockefeller Institute for Medical Research, to secure the answer and also to take up other related laboratory studies which could best be carried on in a fully equipped research laboratory. It was soon shown that the viruses from the various regions were the same and that the serum from persons who had recovered from yellow fever from 30 to 78 years earlier in various countries protected monkeys against the African virus. The studies proved that the historic yellow fever that Reed investigated in Cuba, and the yellow fever that formerly appeared as epidemics in the United States, and the present infection in Africa and South America are all one.

In the meanwhile Theiler at the Harvard Department of Tropical Medicine had independently discovered that the white mouse was susceptible to yellow fever if inoculated in the brain. The Yellow Fever Laboratory of the International Health Division in New York then devised a special protection test in mice and used it in conducting a world-wide survey of human immunity to yellow fever. By mapping the areas in which the blood of the inhabitants protected mice against yellow fever it was possible to tell where the disease had been in recent years, for the immunity thus revealed appears in man only after an attack. Two vast previously unknown endemic areas were discovered by these means, one in Central and West Africa and the other in the Amazon basin and neighboring areas.

Two official international organizations facilitated this survey. The Permanent Committee of the International Public Health Office had sponsored the venture in Africa to the extent of preparing the way with the countries involved and formally requesting The Rockefeller Foundation to undertake the organization and management of the survey. The Health Organisation of the League of Nations called a Conference in Capetown in 1932 at which yellow fever was the principal

subject of discussion, and invited The Rockefeller Foundation to send a representative. This resulted in a splendid opportunity for me to meet the health officers of south and east Africa and arrange for the collection and forwarding of the necessary blood specimens without organizing a special expedition. The survey was an unusual example of effective team work among the health departments of many countries, two international public health organizations, and a private organization in the international field.

After the monkey became available for laboratory work a yellow fever laboratory was set up in Bahia, Brazil. The understanding of the disease was developed rapidly. One amazing discovery was that yellow fever was occurring in the complete absence of the mosquito, *Aedes aegypti*, which had previously been considered the only possible transmitting agent. Further studies in Brazil and Colombia developed evidence that certain mosquitoes and unknown animal hosts were responsible for keeping yellow fever virus alive in the great endemic area of the interior. In fact, yellow fever virus was actually isolated from wild-caught mosquitoes of several species prevalent in the tropical forest. The yellow fever situation in Central Africa soon attracted interest, and fruitful studies were made of the endemic yellow fever which had previously been located only by blood tests for immunity. This work, carried on from a laboratory base in Uganda, has been highly productive, and during the present year (1944) the yellow fever laboratory in West Africa, which had been closed for some time, was reopened for similar studies.

Early in this long series of investigations numerous yellow fever infections of laboratory workers and several deaths made it imperative to concentrate efforts on the search for a method of immunization. An effective vaccine was developed in the Laboratories of the International Health Division in New York and in its first form it proved its value in 1931 by abruptly terminating the series of accidental infections. After improvement which made its wide use practicable it was applied in all the countries in which the Division was participating in yellow fever studies or control, and finally it came into widespread general use for protecting literally millions of civilians and military personnel in regions of possible exposure.

This condensed story is presented here to show how a serious and baffling problem was solved by organizing research in a number of

selected countries, with several laboratories in the field and a base laboratory in New York, and having the whole set-up under a single central administration. The individual scientists could carry their skill and experience from area to area or to the base laboratory when it was to the advantage of the investigation, and current information could be freely exchanged between the individual projects without waiting for publication. The same kind of approach to an outstanding problem could well be made by an official international health organization through advice and assistance to the health experts of many nations.

The Division's studies of influenza also had an interesting international phase. The rapid spread of this spectacular disease from country to country gives it an essentially international character. The possibility that any one laboratory might in a given year have little opportunity to observe the disease nearby and collect material for study of the virus involved, led the Division to locate its influenza projects in widely separated places—New York, Minneapolis, Berkeley, Budapest, and Buenos Aires, with staff members in each for at least part of the time. In addition financial assistance was given to University projects in Ann Arbor and Columbus. Spreading these activities geographically added materially to the knowledge of the epidemiology of influenzas A and B. The memory of the great pandemic of influenza which happened to occur during the last World War, has labeled influenza as an outstanding international health problem, and it is probable, though not proved, that the pandemic disease was at least related to the influenzas that we know today. With the isolation of the viruses responsible for the two commonest influenzas already achieved, and with some encouragement to believe that a method of immunization will soon be developed, we can be confident that we shall not again be so helpless in the face of a sweeping pandemic.

Space will only permit mention of one of the several Commissions which were set up by the League of Nations to stimulate disease investigation and control and particularly to visit places of special interest and evaluate the experience of each for the benefit of the health authorities of all. The Malaria Commission consisted of a body of experts drawn from several nations. Study tours of many malarious regions, from the Mississippi Valley to the Ukraine, were made by members singly or in groups, and reports of great usefulness were made available.

Malaria and its anopheline vectors vary so in characteristics and

behavior that knowledge has to be applied with discrimination and caution, and usually after intensive local study. To speed the acquisition of needed knowledge of this and other diseases and to demonstrate through field trials how it can be applied should be recognized as important functions of any international health organization of the future.

COÖPERATION IN DISEASE CONTROL

In time of war the mention of typhus fever makes one shudder, and a failure to speak of this companion of misfortune and misery would be a glaring omission. With armies taking extreme precautions through immunization and delousing, there probably will be no disasters in the military forces comparable to what befell Napoleon's retreating troops, but it must be expected that international assistance, and plenty of it, will be needed by civilian communities disrupted by war, deprived of soap, limited as to water supply, and with health services disorganized. Many nations, and the American Red Cross as well, gave assistance in fighting the terrible Serbian epidemic of 1915, and the League of Nations' Epidemic Commission took a leading part in 1920-21 in marshaling health agencies for typhus control in Poland.

It should now be possible to work more effectively than during and after the last war, for methods have been improved, and health organization has been developed. With the new and highly effective insecticidal powders, and the simplified methods of application by blowing them through the hair and clothing, it will be practicable to set up an organization within the local health department which can treat infested people in their homes or at convenient health centers and prevent the transmission of typhus. The activity could be systematically controlled by louse counts and indices so that the local extermination of the insect would be expeditiously accomplished and its continued absence insured. By such methods typhus has already been stopped abruptly in institutions and communities. The old methods of clipping the hair and steaming the clothes, often ruining cherished articles, can be relegated to history along with the resistance they inspired. The newer methods were given preliminary trials in Mexico and North Africa by the International Health Division with the coöperation of local health authorities. The response of the people to this opportunity for relief from lice is uniformly favorable, even when the fear of typhus has ceased, and sometimes the insistent demands are almost overwhelming.

This eagerness to get completely rid of lice is in sharp contradiction to cynical prophesies which had been made to us. It had been predicted that the people would resist because of a superstition that some degree of lousiness was necessary for health. This slander probably has as little foundation as the oft-quoted belief of some of our reactionaries that if you gave bathtubs to tenement dwellers they would be used for storing coal. In one country the prevailing attitude was well illustrated by a grateful woman who returned the day after her clothing had been powdered to say that she was fifty years old and that for the first time she had slept through the night without awakening to scratch. No wonder that the insecticide has even been referred to as a sleeping powder or that a boy was caught pilfering it for sale at a high price on the black market.

Dr. F. L. Soper, of the staff of the International Health Division, after having successfully directed campaigns for the eradication of *Anopheles gambiae* and *Aedes aegypti*, is now enthusiastically applying extermination techniques to the louse. Some months ago he reported from a foreign country that since the necessity for removing clothing before administering the powder had been obviated it was possible to apply the insecticides in homes, schools, courtyards, and a garage—"just wherever it was possible to find two or three lousy ones gathered together." On one Saturday the entire population of a district, according to the local authorities, came to two points on the automobile highway to be powdered. As the result of the continuing investigation and experience of the International Health Division, the United States of America Typhus Commission, and health officials in various countries, it should be possible after the war to take a world view of the typhus situation and get rid of the louse-borne disease wherever it has become entrenched. Vaccination, which at least diminishes mortality, would be an additional weapon in fighting typhus.

A dying man with weakened heart and swollen legs, a sufferer from beriberi contracted by eating over-polished rice, is just as much the victim of preventable disease and community neglect as if he were succumbing to cholera or typhoid. Now that the causes of nutritional deficiencies are becoming better understood and their correction is more practicable, the diseases of malnutrition are slowly beginning to take their rightful place beside those caused by infection as responsibilities of the public health authorities. Field investigations are becoming more

practical and productive, and as a result useful knowledge is accumulating. Nutritional disease requires the same types of investigation—clinical, physiological, epidemiological, and laboratory—as do the other diseases studied by health departments. After a prevalent nutritional deficiency has been investigated and identified by the health authorities, the correction of the causes in the community often involves coöperation with agencies interested in economics and agriculture. The responsibility for the trouble is frequently shared by other countries and international coöperation is therefore necessary. A great impetus to the movement to investigate and improve nutrition was given by the League of Nations' Mixed Committee on the Relation of Nutrition to Health, Agriculture, and Economic Policy, which brought out its final report in 1937. Another important step has just been taken by the United Nations Conference on Food and Agriculture, at which the decision was reached to set up a permanent international organization in the field of food and agriculture. This organization dealing with many subjects besides human nutrition should be a source of help and strength to the technical groups interested in nutrition in an international health organization.

DISTRIBUTION OF CURRENT INFORMATION

Any future official international health organization will, I hope, follow the example of the League's Health Organisation in its excellent system of collecting and distributing current health information for the benefit of all countries. The Epidemiological Reports appeared quarterly and gave statistical tables showing for many countries the reported cases of important diseases and the deaths. To me the most useful information was in its summaries giving the accumulated information on the epidemiology, distribution, and control of various diseases of special interest. These reviews were in English and French and were accompanied by informative maps. This publication has stopped, but reviews of specific diseases are still appearing in the Bulletin of the Health Organisation, and the Weekly Epidemiological Record is arriving as a leaflet. At the height of its activity the League maintained a Far Eastern Branch Office which received health reports from eastern countries and from ships and broadcast the information by radio. To gather and prepare the statistical and epidemiological material, there was in the Health Section of the League an effective Service of Epidemiological

Intelligence and Public Health Statistics. Through such a system of collection and publication all the world could receive prompt notice of health events as they happened and could be forewarned of new disease hazards.

FACILITATING PROFESSIONAL EDUCATION IN PUBLIC HEALTH

International health activities have as their ultimate aim the establishment of efficient health administrations in all the countries of the world. This end will be approached only when the directing personnel in each country consists of full-time trained health officials who have had education and experience in their fields and know what is going on in the rest of the world. Perhaps the greatest opportunity of an international health organization would be to take part in the professional education of persons who will be holding important public health positions. For every country some of these men should be trained in foreign lands or should be given opportunity to travel and compare their own methods with those of other officials visited. Younger men usually profit from a postgraduate course in a School of Public Health and this may require fellowships from an international agency.

The League of Nations called its activities in this field "*interchanges*." Two methods were followed. In one, a public health officer or some one appointed to a future public health position was given facilities for studying in foreign countries. In the other, "collective interchanges" were arranged, and groups of medical health officers from different countries were taken on a supervised tour of study of health problems and methods, sometimes limited to one specialty within the public health field.

The International Health Division spends most of its educational funds on fellowships under which promising young persons who are already in public health work or are assured of an appointment, are given courses in a School of Public Health in the United States or other country away from home. Former fellows are now scattered over the world, and those in the occupied countries of Europe will be extremely useful when the war is over and health departments are being reorganized and developed. In traveling about the world one gets the impression that the men trained under fellowships are the greatest and most lasting asset that many countries have received through their co-operation with the International Health Division. The travel grants of

the Division are for the more mature officials, who require only an opportunity to visit their colleagues in foreign lands to compare methods and exchange the results of experiences. The benefit is usually shared by the person visited. By-products are an increased interest in international coöperation and a valuable acquaintance among persons carrying similar responsibilities.

INTERNATIONAL STANDARDIZATION

Many of us have been irritated during our travels by the lack of international agreement on rules of the road, alphabets, and weights and measures. Even in the health field the lack of standardization may be annoying and even dangerous. We can thank the League of Nations for bringing about uniformity in the standardization of curative and protective sera, hormones, and other biologics, and even vitamins and some drugs. The League's Permanent Commission on Biological Standardization has carried the responsibility for this activity. Standard preparations have been sent periodically to many countries for use in keeping the local units of strength in agreement with those adopted internationally. Before the League was established international commissions were already preparing and revising the International List of Causes of Death. Doubtless in other matters it will be found that international standardization is necessary to prevent dangerous variation among the units and terms in use in different countries.

SOME FUNDAMENTAL PRINCIPLES

For a maximum of success there are certain principles which should be observed by any international health organization that might be set up after the war:

It should help and advise the technical health officials of the several nations and facilitate coöperation among them, but without assuming to be a superimposed agency directing their work.

Full-time service, with salaries consistent with such service, should be advocated, and educational assistance should be made conditional on such service.

Enslavement by routine should be avoided. The first aim should be to lead in searching out and defining important health needs, anticipating dangerous situations, and devising more effective methods than those we now have for protecting and improving health.

Dealings should be directly with technical health officials, and the activities of the international health organization should be free from secondary political ends. In international coöperation in the health field all effort should be concentrated on the one enemy who has no friends—disease.

THE FUTURE

The world has shrunk greatly since the early days of ship quarantine. Measured in travel time every region is now close to every other. National barriers at frontiers are increasingly futile, whether they be military fortifications, high tariffs, or rigid quarantine. In each case international coöperation for common benefit is the only possible substitute.

Before making a forecast of anticipated progress in international health procedure it might be profitable to summarize its evolution up to the present. In the first stage there was only quarantine against a few pestilential diseases. In the second, there was more knowledge as to the nature of diseases and the manner of their spread, and a growing tendency for nations to act in concert in controlling the more serious ones, like plague, in the ports of origin as well as through quarantine. The third and present stage finds conventional quarantine in a minor place. The terror and helplessness inspired by many diseases have largely disappeared. More diseases can be suppressed through immunization; many insect vectors are now known and controlled; the influence of social and economic factors and nutrition in ill health are becoming better understood; and as a result of all this the procedures of prevention are becoming more diverse, highly technical, and increasingly efficient.

At the present moment the war interest has forced greater attention to the exotic diseases and has revealed the relative neglect with which our medical teaching has treated the maladies peculiar to our neighbors on this contracting globe. Steps are being taken to correct this. Since the first World War an invaluable experience in international health relations has been accumulated in many a country and a nucleus formed of trained health experts, including a growing body of public health nurses. These assets will count in the next advance, but they will have to be multiplied.

The fourth stage is in the future, and we can only speculate about it. There will probably be still less reliance on conventional quarantine

and more on the control of disease wherever it is discovered. As such control will be for universal benefit, we hope that it will be fitted into a world plan, formulated internationally, and that expert or financial assistance, needed by the national health authorities in any country, will somehow be made available by the central organization. It is of world-wide importance, for example, that the control of yellow fever should be centered in the endemic areas of Africa and South America and supported by the combined agency of all the benefiting countries. When world strategy requires that an intensive fight must be made in some country to keep it from becoming a stepping stone for a disease or insect vector, like *Anopheles gambiae*, toward other lands, then the world should be ready to help direct the effort and pay for it.

Is it too much to hope that the central organization through its conferences will direct attention to the universal distribution of mental disease, the common cold, and dental caries, evaluating their importance and using its influence and support to stimulate the research which will have to precede effective prevention?

Just as we expect the world to organize to prevent war anywhere before it gets started, so we look forward to the time when all countries will combine to extinguish the sparks of pestilence before the flames begin to spread, and to obtain the knowledge necessary for action. This would be far easier than to let diseases rage here and there and then try to stop them at a thousand boundaries.

We can hope and expect that the rehabilitation function of the United Nations Relief and Rehabilitation Administration in the field of health will be so exercised as to encourage the rapid recovery or re-establishment of self-reliant national health departments and to demonstrate the advantages of international coöperation. Then should follow the golden opportunities that will come with peace. We envisage a world with many active national health departments, each of which meets its responsibilities to its own country, enters into organized coöperation with the other nations, and plots an unending war against disease under the generalship of a strategy board for the world.

CLINICAL RESEARCH MEETING

Arranged by the Committee on Medical Education

APRIL 5, 1944

MEDICAL DIVISION

BERNARD S. OPPENHEIMER, Presiding Officer

* * *

Effect of Liver Disease on Vitamin A Absorption

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The liver has an important function in the metabolism of Vitamin A. It converts the provitamin carotene into the vitamin and is the chief depot of the latter. Marked changes of Vitamin A metabolism are found in liver disease.

In normal individuals the "fasting" Vitamin A blood level remains constant with normal nutrition. In acute hepatitis, cirrhosis of liver and other forms of liver damage, e.g., in mechanical obstruction with superimposed parenchymal damage, the blood Vitamin A figures are low and return gradually to the normal level in the recovery phase. There exists, however, no strict parallel between the extent of hepatic damage, as evaluated by the various liver function tests (blood cholesterol, esterified cholesterol, galactose tolerance, cephalin flocculation, prothrombine time, icterus index, etc.) and the lowering of the Vitamin A level.

The response to the oral administration of a test dose of Vitamin A (Vitamin A Tolerance Test) was studied in 50 cases of liver disease and many controls. In partial biliary obstruction (stone, neoplasm) and in compensated cirrhosis the response is usually normal. In acute hepatitis, cirrhosis with superimposed hepatitis, and in prolonged biliary obstruction, the postprandial elevation of Vitamin A in the blood is reduced or completely absent. The character of the curves varies with the nature of the hepatic disease, the stage of the disease, and the extent of hepatic damage. Evidence is accumulating that the flat curves in liver disease are caused by impaired intestinal absorption and perhaps by depletion of Vitamin A reserves in the liver. In the recovery stage normal or even abnormally high curves are observed, suggesting satisfactory intestinal absorption but insufficient deposition in the liver.

* * *

*A Qualitative Change in Serum Albumin in Parenchymal Liver Disease*DAVID B. MOORE, PAUL S. PIERSON, DAN H. MOORE, and
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Kabat et al., in 1943, reported studies on the reaction of cephalin-cholesterol emulsions and colloidal gold suspensions with various

fractions of normal and pathological sera as obtained by electrophoretic separation and showed (1) gamma globulin from normal

and pathological sera (parenchymal liver disease) causes comparable flocculations, whereas no other protein component of the serum gives the flocculation reaction and (2) normal albumin inhibits the colloidal gold reaction with gamma globulin but not the cephalin flocculation. The purpose of this paper is to report further investigation of electrophoretically separated protein fractions from the sera of normal persons and of sera from patients with parenchymal liver disease, over a wider range of concentrations than those used by Kabat and his collaborators.

The investigation was conducted using the sera from 2 patients (catarrhal jaundice and arsphenamin hepatitis) and 1 normal subject. The cephalin flocculation was done as described by Hanger using varying amounts of protein components. Separation of the protein fractions was carried out in the Tiselius apparatus and the concentration of each fraction determined by measuring its refractivity in a previously calibrated Zeiss interferometer.

The procedure followed was:

1. Knowing that an excess of normal serum inhibits flocculation of abnormal serum, the range at which complete inhibition occurs was established.

2. The concentration of the various protein fractions within the effective inhibiting range was determined.

3. We were then able to duplicate the conditions of inhibition using amounts of either normal albumin or abnormal albumin comparable to the albumin in the inhibiting serum, against amounts of gamma globulin

comparable to the gamma globulin in the flocculating serum.

It was found that normal albumin inhibits completely the flocculation of gamma globulin in the proportions used, whereas identical amounts of albumin from cases of parenchymatous liver disease showed little if any inhibiting properties. Table II.

The albumin from all sources showed no flocculating properties. We have further confirmed the findings of Kabat et al that the gamma globulin in health and liver disease shows identical flocculating capacities. Table I.

The evidence presented points to qualitative changes in the albumin fraction in parenchymatous liver disease in that the inhibiting properties of normal albumin are not observed in this abnormal albumin. It is significant that crystallized normal human serum albumin fails to inhibit the flocculation of gamma globulin. The nature of these changes is now under investigation.

TABLE I—EFFECTS OF VARIOUS SERUM COMPONENTS ON THE CEPHALIN FLOCCULATION REACTION

| | <i>Normal Patient</i> | <i>Hepatitis Patient</i> |
|----------------------------|-----------------------|--------------------------|
| Whole serum .. | 0 | ++++ |
| W Serum albumin | 0 | 0 |
| Serum gamma globulin | ++++ | ++++ |

TABLE II—THE INHIBITING POWERS OF ALBUMIN FROM NORMAL SERUM AND HEPATITIS SERUM IN THE FLOCCULATION OF GAMMA GLOBULIN

| | <i>Gamma globulin in diminishing amounts</i> | | | | |
|--|--|------|------|------|------|
| | 0.1 | 0.08 | 0.06 | 0.04 | 0.02 |
| No serum albumin added..... | ++++ | ++++ | +++ | ++ | 0 |
| Albumin from normal serum added..... | 0 | 0 | 0 | 0 | 0 |
| Albumin from hepatitis serum added.. . . . | +++ | +++ | + | 0 | 0 |

Nocturnal Secretion Studies in Normals and in Patients with Peptic Ulcer*

ALBERT CORNELL, ASHER WINKELSTEIN and FRANKLIN HOLLANDER

In 1928, Chalfen¹ showed that nocturnal secretion in normal persons was lacking in free hydrochloric acid, or, if present, was only minimal in amount. Winkelstein² confirmed these findings and also found a marked increase in the quantity and concentration of free hydrochloric acid in patients with peptic ulcer, especially those with duodenal ulcer. In 1932 and 1933 Henning and Norpoth³ confirmed these latter observations, as did Val Dez⁴ in 1942. Recently, however, Sandweiss⁵ and his co-workers reported that both normal subjects and patients with duodenal ulcer secreted acid gastric juice although a greater quantity of juice was aspirated from the patients with ulcer. Because of such opposing views, chiefly with reference to the findings in normals, further studies have been carried out at The Mount Sinai Hospital since 1938. The purpose of this communication is to present these studies.

The normal subjects consisted of 9 males without any history of gastrointestinal dis-

turbances admitted to the hospital for a herniorrhaphy or similar procedure. The older age group was eliminated so as not to introduce possible achlorhydria due to age alone. The patients with peptic ulcer were those with uncomplicated duodenal ulcer, proven by x-ray or operation. In this group there were 16 test meals carried out on 14 patients.

From our studies, we conclude that patients with uncomplicated duodenal ulcer reveal a large amount of highly acid secretion during the night. Normal subjects showed little or no free hydrochloric acid and specimens were difficult to obtain in most instances because of the small amount of night secretion.

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Cold Hemagglutination and Cold Hemolysis

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The association of cold agglutination of erythrocytes with some cases of non-syphilitic paroxysmal cold hemoglobinuria and hemolytic anemia has been known for years. However, the mechanism by which cold hemagglutination leads to hemolysis had not been elucidated previously.

The studies show that the hemolysis which is dependent upon cold hemagglutination is due jointly to a high titer (over 1/3000) of cold hemagglutinins, a high concentration of erythrocytes in the reacting mixture and mechanical trauma brought about by shaking or tapping. There is a direct linear relationship between the cold hemagglutinin titer and the cold hemolysin titer. Comple-

ment action is not necessary for hemolysis. The slightest amount of agitation of strongly agglutinated blood is followed by hemolysis.

Using an apparatus consisting of a 3-foot length of capillary glass tubing immersed in ice water, it is shown that the mechanical trauma due to the injection through this tube of blood containing potent cold hemagglutinin is enough to cause intense hemolysis. Numerous controls of this test have been carried out successfully.

The immersion in cold water of an extremity of a patient whose blood contains potent cold hemagglutinins causes intravascular hemolysis.

Antibody Production After Antigenic Pneumococcic Polysaccharides in Man and in Animals

Relationship Between Nutritional Deficiencies, Contributory Diseases and Resistance to Infection

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To test the antigenic properties of the polysaccharide used in this work¹ a group of mice were injected in the peritoneum with $\frac{1}{2}$ cc. of 1:1,000,000 solution and 8 days later dilutions of pneumococcus culture were injected in the abdominal cavity. Protection was found in 50 per cent of the mice against 1-5,000,000 lethal doses. Since in the mouse-protection tests the animals die of bacteremia before pneumonia develops, in another set of experiments the question was examined whether the antigen gives protection against experimental pneumonia. Method used was similar to the one of Stillman and Branch:² animals were exposed to infection in a closed box sprayed with 10 cc. of virulent pneumococcus solution; pneumonia developed only in 2 per cent of the animals. If, however, they were previously intoxicated with intraperitoneal alcohol injection or with ether inhalation, 20-50 per cent developed pneumonia. Of the animals who received $\frac{1}{2}$ cc. of 1:1,000,000 dilutions of antigen and similarly treated, all except 5 per cent remained healthy.

In the five years 1937-1942 an experiment in which 9,070 individuals were involved was done. Half of them were injected with the antigen and the other half were kept as controls. In the first two years every 20th person was bled before and 14 days after the antigen and the protective antibodies of 0.10 cc. of the sera titrated in mice.

Results: a) Sixty-five per cent of the immunized showed a hundredfold increase of protective bodies; b) in five years the incidence of pneumonia was less than one-half among the immunized as compared to the controls (16.5 per cent against 38.6 per cent); c) the mortality rate was about one-third among the immunized of that of the control group. Since, however, our fig-

ures indicate great fluctuation in the number of pneumonias from one year to the other, we believe that this type of experiment permits definite conclusions only if conducted for about 6 to 10 years.

There were indications in our work that those who were not able to manufacture antibodies were more prone to pneumonia infection than the ones who were able to do so. It also seemed that the percentage of negative reactors was considerably higher in the group investigated than in the general population. The next step was to examine the possible causes of this and of the high incidence of pneumonia in institutionalized individuals and among the aged. A survey of nutritional deficiencies was made by study of hospital charts, diets, medical, laboratory and biomicroscopic examinations in both negative and positive reactors. Also a survey was made of the inter-relationship between deficiency states and certain conditioning diseases. Results: a) 93 per cent of the investigated old individuals showed one or more signs of nutritional deficiencies; b) somewhat higher was the prevalence of deficiency states among the negative than positive reactors; c) the relationship between vitamin deficiency states and certain conditions (liver damage, nephrosis, long-standing decompensated heart failure, anemias, achlorhydria, general malnutrition) was suggestive of a reciprocal action, i. e., the diseases are contributory factors in the development of deficiency states and the deficiencies produce or aggravate these diseases. Other than nutritional causes of high incidence of pneumonia in the group investigated were also examined and found probably to be: crowding, presence of carriers, diminished cough reflex, frequency of conditioning diseases and general decline of

the defense mechanism in the aged. At this phase we also investigated the problem whether optimal diet and optimal doses of vitamins increase the ability of the negative reactors to manufacture antibodies in a higher degree than before. The individuals were "vitaminized" for 4 weeks, bled, then pneumococcus polysaccharide was injected and 2 weeks later they were bled again. Both batches of sera were titrated for their mouse protective contents against dilutions

of pneumococci. Results: a) there was improvement in a great number of the deficiency signs; b) the protective titer increased only in 3 out of 58, which statistically is not significant.

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The Treatment of Filariasis (Wuchereria Bancrofti) with Anthiomaline

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Recent military medical reports indicate that men in the theaters of war are exposed to filaria infections and a number of them have become infected. The therapy of filariasis has been unsatisfactory but recent therapeutic trials of anthiomaline, an anti-mony compound, in human filarial infections indicate that this drug may be effective. A number of persons exhibiting *Wuchereria*

bancrofti microfilaria in their blood were treated with intramuscular injections of anthiomaline and their microfilaria counts were reduced 85 to 100 per cent. These cases have now been followed for six months without relapses among the group. The toxicity of the drug to man is sufficiently low to warrant its continued trial in the early stage of filaria infection.

* * *

*Clinical Arrest of Bacterial Endocarditis by Bacteriostatic Agents, Particularly Penicillin**

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In the experimental endocarditis of rabbits, induced by intravenous injection of cultures of streptococci of the viridans group, healing and healed lesions of the disease have been observed following the therapeutic use of anti-infectious agents. The early defense against the infection depends chiefly upon phagocytosis and digestion of the bacteria by vascular endothelium and wandering leukocytes. At the sites of more severe injury, as on the heart valves where physical stress and pressure aids the

infectious agents, there is deposit of fibrin in which the bacteria may multiply abundantly. Subsequent limitation and healing of these infected thrombotic deposits is favored by (1) bacteriolysis, (2) phagocytosis and (3) encapsulation and scar formation. Restraint of rapid bacterial multiplication is evidently essential to the success of the healing processes and hence there is easily recognized the therapeutic need of (1) physiological rest (2) anti-infectious agents in the circulating blood and (3) adequate nu-

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trition for the defending cells.

Some anti-infectious agents of chemical and of biological origin have shown significant effects upon the bacterial cultures *in vitro* and their use in experimentally infected animals has in some instances been followed by observation of healing and healed lesions of endocarditis. Application of these observations in therapy of the human disease could not be delayed. One example of apparent arrest in which there was a long period of deterioration approaching the terminal stage followed by a successful program of treatment, may be briefly presented at this time.

M. F., female, 32, developed endocarditis following dental extraction on February 22, 1943, with mitral murmur, recurrent petechiae, persistent positive blood cultures, embolic lesions of brain, retinae and spleen, hematuria and extreme emaciation, in spite of treatment with sulfadiazine, thiobis-

mol, neoarsphenamine and multiple small transfusions. A very small supply of partially processed penicillin became available on June 23 and this seemed to have a slight beneficial effect without halting the progressive down-hill course of the disease. However, on September 15 the use of more adequate amounts of penicillin was followed by dramatic clinical improvement. The blood culture taken on September 20 remained sterile as did all subsequent cultures of the blood. Penicillin was continued in doses of 5,000 units every 2 hours, with some variations, until January 7, then reduced to 3,000 units and on January 10 to 1,000 units. It was finally discontinued on January 17. The total penicillin expended was approximately 4,864,000 units. The patient has regained her normal weight and appears well except for persistent moderate weakness of legs, ankles and feet. This does not prevent walking.

* * *

Combined Penicillin and Heparin Treatment of Subacute Bacterial Endocarditis¹

LEO LOEWE, PHILIP ROSENBLATT, HARRY J. GREENE and
MORTIMER RUSSELL

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A conjoint chemotherapeutic and anticoagulant attack has been effective in causing the disappearance of experimental thrombotic endocarditic lesions.² Results with sulfonamides and heparin in human cases of subacute bacterial endocarditis have been disappointing. When penicillin was substituted as the chemotherapeutic agent in the combined treatment the results were striking and consistent.

The dosage schedule for both penicillin and heparin has been worked out. The penicillin was given mostly by continuous venoclysis. The heparin was administered either by a specially devised subcutaneous method³ or by venoclysis in combination

with the penicillin.

Seven out of eight cases in the initial series were successfully treated; that is, the blood stream became bacteria free and the patients exhibited marked, progressive clinical improvement. In contrast with sulfonamides, the treatment has minimal toxicity and is well tolerated. Twenty-two additional patients have been or are being treated with similar promising results.

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Thiouracil in the Treatment of Postoperative Recurrent Toxic Goiter

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Recurrence of toxic goiter after a subtotal thyroidectomy presents a difficult problem in therapy. In many instances further operation is inadvisable, and radiotherapy or iodine may not stop the overactivity of the gland.

The results of thiouracil therapy in a series of 13 cases of recurrent hyperthyroidism of this nature, and 2 more cases of exophthalmos are reported here. These have been successfully treated in the thyroid clinics of the Vanderbilt Clinic and in the Presbyterian Hospital, for more than 4 months at the present time. Toxic symp-

toms from the drug have been few, but, when present, severe enough to warrant stopping treatment. A fair amount of variability is found in the dosages needed to reduce the basal metabolic rate to normal and to maintain this lowered level. The effect of the drug upon the basal metabolic rate, fasting serum cholesterol, symptoms and physical signs is to restore these to normal. Exophthalmos may progress during thiouracil therapy. Caution in the use of thiouracil and very careful watch over the blood count are necessary in using this treatment.

* * *

The Effect of Certain Liver Extracts on the Carbohydrate Metabolism (Clinical and Experimental Study)

HENRY B. SOKAL, Brooklyn and JOSEPH E. SOKAL, New Haven Hospital

The question of the effect of liver extract on the carbohydrate metabolism was revived when Blotner and Murphy published in 1929 a paper in which they claimed an insulin like action of liver and liver extract on the blood sugar in the human, and especially in those suffering from diabetes.

Later investigations carried out by a number of workers not only failed to support these claims, but on the contrary it became evident that a definite rise in the blood sugar occurred following the administration of certain liver extracts. This was noted in man as well as in the experimental animal.

Henry B. Sokal's experience with the effect of liver extract on the carbohydrate metabolism in man goes back to the year of 1932. At that time seventeen patients suffering from pernicious anemia were treated by him with an extract supplied for clinical use by the Wilson Laboratories in Chicago.

He used two extracts, fraction "A" and

fraction "B." Both were intended for parenteral use, and supplied in individual 5cc. ampules. To test the potency of both fractions the patients were divided into two groups; one group receiving regularly fraction "A," while the other was treated with the fraction "B" extract.

After some weeks of treatment, one patient, a woman about 60 years old, began to complain of a severe and persistent itch in the vulva. Examination of the urine showed the presence of a reducing substance and the blood sugar was 150 mg./100 cc. A blood sugar examination made about six months previously during the patient's stay in the hospital was recorded at 90 mg., and the urine at that time was negative.

Since the coexistence of pernicious anemia and diabetes mellitus was always regarded as a very rare occurrence, he assumed that the liver extract was in some way responsible for the appearance of these changes. To make sure that this was not a mere

coincidence he examined the urines and blood sugars of several other patients who were then under the treatment with this extract. The results of these examinations confirmed his suspicions. All patients treated with the fraction "B" of the extract had glycosuria and an elevated blood sugar. Continuation of the treatment caused a gradual rise in the blood sugar, until after several months of treatment the blood sugar reached the level of 320 mg./100 cc.

In several patients he had the opportunity to determine the level of the blood sugar just before starting them on this extract. After 6-8 injections with the fraction "B" of the liver extract a 50 per cent increase in the blood sugar was the rule.

His resignation from the clinic postponed further work on this problem until 1937, when Dr. Long of the Yale Medical School was kind enough to extend the facilities of his Department for the experimental study carried out there by his son, Joseph E. Sokal.

As a preliminary to the experimental study six commercial liver preparations were examined for their ability to produce glycosuria and hyperglycemia; no attempt was made to find an extract capable of reducing the blood sugar. A complete chemical study of the extracts was made. In general they were water soluble, free of protein and contained the equivalent of about 14 per cent of glucose. Normal mice, guinea-pigs, and rats were used in these experiments. Studies were also carried out on adrenalectomized rats, on latent diabetic rats and in one frankly diabetic rat.

Daily determinations of urinary glucose over long periods, both during the administration of liver extract and during control periods were made in all animals used in

this study. The effect of liver extract on the blood sugar levels was studied during the fasting state as well as in the absorptive and postabsorptive state.

In a number of animals studies were carried out on the effect of insulin on the hyperglycemia produced by the administration of the liver extract. Investigations were also made on the effect of liver extract on the carbohydrate stores in normal animals in the fasting and absorptive state. Other studies made during these experiments were: The effect of liver extract on the nitrogen balance and on the respiratory quotients in normal and diabetic animals in the fasting state and during the absorption of glucose. Finally attempts were made to isolate the glycogenolytic principle.

In the course of these investigations it was proven conclusively that by injection of Wilson's liver extract fraction "A" and "B," glycosuria and hyperglycemia were produced in every instance. A marked decrease in the liver glycogen, and to a lesser degree in the muscle glycogen resulted from the administration of the extract. On autopsies no deviation from the normal microscopic appearance was found.

SUMMARY

The existence in some liver extracts of a substance capable of producing glycogenolysis, glycosuria, and hyperglycemia in the normal rat has been demonstrated. The glycogenolytic principle is water soluble, heat stable and dialysable through cellophane. It is not a protein. It is less active by mouth than parenterally. It is resistant to acid, although it loses some activity in alkali. A partial purification has been accomplished.

* * *

Experimental Gastric Lesions Produced by Calcium Deficiency

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Rats fed a calcium deficient diet develop lesions in the antrum of the stomach that resemble certain forms of gastric ulceration

in man. The pathological changes in the mucosa of the antrum consist of hemorrhagic ulcerations in areas of epithelial hyper-

plasia that tend to undergo spontaneous healing. Recurrent hemorrhage and necrosis occur in healing defects. Lesions appear after the second or third week of the deficiency but are most numerous after four weeks. When experiments are continued for eight weeks the ulcerations are larger and more hemorrhagic but do not penetrate the muscularis mucosae. Addition

of calcium to the diet results in rapid repair of epithelial defects and complete regeneration of glands. Scarring does not occur within the time limits covered by these experiments. Preliminary studies on the circulation in the mucosa indicate that calcium deficiency has an effect on the capillaries.

* * *

The Experimental Production of Recurrent Convulsive Seizures in the Monkey

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New York State Psychiatric Institute

Acute, intermittent, and recurrent convulsive seizures have been induced in the rhesus monkey by the single application of discs containing various chemical and immunologically active substances to the cerebral cortex overlying the motor area. The recurrent seizures have been either Jacksonian or generalized in type and have been elicited in some animals for more than two years to date. Hydrous oxides of aluminum invariably produced recurrent seizures. Other preparations such as egg-white, typhoid vaccine, etc. were not so uniformly successful. Control preparations of aquaphor, alone or in combination with other proteins, as well as empty discs, applied to

the motor cortex, failed to induce seizures in animals similarly operated.

Electric shock was used to elicit contralateral focal reactions and electroencephalographic records indicated a focus. Luminal was effective in reducing or preventing seizures. Histopathologic findings and serologic studies failed to reveal significant changes in the brain or serum of reacting as compared with non-reacting animals.

The repeated convulsive seizures which have been produced by a single application of chemical or immunologic substances to the cerebral cortex offer a means of studying further the nature of the convulsive state and its treatment.

* * *

The Electrocardiographic Diagnosis of Right Ventricular Hypertrophy

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Study of right ventricular hypertrophy has heretofore been unsatisfactory because of several reasons, one of which is the fact that multiple precordial leads, especially those near the sternum, are not in proper relation to the main muscle mass of the right ventricle.

On the basis of anatomical observations,

and after an investigation of unipolar electrocardiograms in adults taken from about 30 different areas of the body, we found that the unipolar lead taken from the right upper abdominal wall is of distinct value in determining right ventricular hypertrophy, even of moderate extent.¹

To understand how this lead is of value,

* Work done in part under a Fellowship of the Martha G. Hall Foundation.

the following explanation is necessary: the ventricles may be considered as a cup-shaped muscle mass. The wave of activation spreads through the ventricles from within, outward. Since the wave of activation has a (+) pole in the direction in which the wave is spreading, theoretically, a lead over the left ventricle should record a (+) potential; and a lead over the right ventricle should also record a (+) potential. This occurs in children where the relative sizes of the right and left ventricles are similar. In adults, the left ventricle is

much larger than the right, and the right upper abdominal lead, instead of being (+) is small and iso-electric. However, when right ventricular hypertrophy occurs, the right upper abdominal lead becomes (+), even when there is no change in the electrical axis of the standard leads; and in those cases of right ventricular hypertrophy in which the precordial leads have heretofore not been characteristic.

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* * *

SURGICAL DIVISION

RAYMOND P. SULLIVAN, Presiding Officer

Ultra Violet as an Auxiliary in Eye Biomicroscopy

GEORGES KLEEFELD

Structures of the living eye can be studied microscopically thanks to the invention of the slit lamp. The fluorescence of the eye, exposed to Wood light, retained the attention of research men, among them Hague, Feldman, and Van Lint.

In 1927, Duke Elder published the description of his ultra violet slit lamp, wherein the Nitra bulb was replaced by a mercury low pressure vapor tube. The optic lenses were made of quartz. The light was filtered by a sheet of Wood glass.

In fact, the rays of A 3660, which are those provoking fluorescence, are not intercepted by the optic glass used for making lenses. This simplifies the problem considerably, because the average equipment can be used for the routine examination and fluorescence as well.

Since 1927 new improvements have been brought to the tubes. My research work started in 1939, so that in April 1940 I was able to show the fluorescence in the eye when exposed to the very powerful light of the high pressure mercury vapor arc. It is a tube very similar to that I used for the present research work. The power was increased by a reflector. Visible light and

short ultra violet were cut off by a Corning or a pyrex filter transmitting A 3660. It is of great importance to insist upon the fact that this light is considered as harmless. For myself, I have never suffered from exposure, nor have the persons examined.

Equipment: The ultra violet lamp is attached to a swinging arm, in order to bring the former more or less close to the patient's eye; his chin rests upon the proper part of the unit, which consists besides of a slit lamp and a binocular microscope.

Technique: The eye is always observed through the microscope; it is exposed to the light of the ultra violet lamp, or to that of the slit lamp, or to both together. Sometimes a red filter is inserted in the slit lamp beam when the last kind of examination takes place.

Some observations and results:

1. The emission of filtered light suffices for the examination of the skin, the conjunctiva, the cornea, the iris and the anterior part of the lens. It allows the removal of concretions in the conjunctiva. It provokes a pupillomotor reaction.

2. The *Dark Light* is emitted after passage through a purple filter. This filter

reflects upon the skin, the conjunctiva and the cornea, so that there is a discoloration of the latter.

3. The reports of previous observers about fluorescence of the lens, cornea and conglomerates were confirmed also.

4. In addition, the keratic precipitates are visible in ultra violet.

5. Pigment deposits laying upon the crystalloid are easily studied in U.V. and become more visible in combined light with addition of a red filter. The same is to be said about the posterior synechiae. Further observations will prove that the pigment located behind the capsule will disappear in U.V., e.g., in siderosis of the lens. When pigment of the retinal layer of the iris disappears at the iris border of the pupil, this is easily seen in U.V.

6. Foreign bodies of the cornea become

obvious upon the fluorescent background of the lens, in U.V.

7. There is a pigmentation of the cornea that is not perceivable in routine slit lamp examination. Its origin has not yet been established.

Besides, the so-called "Staehli line" and the "Fleischer line" of keratoconus are much more extended than can be seen at the routine slit lamp examination.

8. As diagnostic dye stuffs, I studied fluorescein, bengal rose, magdala red, mercurochrome and rhodamine. In U.V., rhodamine draws the limits of the epitheliolysis; fluorescein alone adheres to the exulcerated places and creeps under the epitheliolysis zone; bengal rose does not fluoresce, and stains the lesion exactly; a double staining with fluorescein is thus very interesting.

* * *

The Treatment of Burn Shock with Sodium Lactate— A Year's Experience at Babies Hospital and Harlem Hospital

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the Babies Hospital, and Harlem Hospital

The shock syndrome which follows severe burns is accompanied by hemoconcentration and diminished plasma volume. Treatment with solutions of crystalloids has recently been supplanted by the administration of plasma and its derivatives. Further study shows that the problem is more complicated.

Recent experiments suggest that electrolytes deserve reconsideration.^{1, 2} Accordingly sodium lactate has been administered to treat shock accompanying severe extensive third degree burns at Harlem Hospital and Babies Hospital.

Sodium was given orally as isotonic (1.75%) sodium lactate solution; 125 cc. per kilogram body weight given in the first 24 hours. This amount was reduced as the

urinary output reached normal. In severe burns, the lactate was given by a Levine tube; occasionally isotonic sodium chloride was given intravenously for a short time to combat transient circulatory collapse. Vomiting occurred in some cases; urinary secretion usually began a few hours after treatment was instituted and azotemia and albuminuria did not occur. When the urine became alkaline on the second day, a mixture of isotonic solution of sodium lactate and sodium chloride was used.

Laboratory studies showed lowered concentration of sodium in the plasma and a reduced excretion of sodium and chloride in the urine despite the large sodium intake and copious urinary output. This discrepancy is explained by experiments with radiosodium in mice which showed the piling up of sodium in burned and traumatized tissues.

In the two hospitals there were 64 burns,

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development, and the Columbia University College of Physicians and Surgeons.

28 of which required skin grafting. There were 5 deaths: two occurred within 4 hours in burns involving over 80% of body surface, another occurred one week after the first skin grafting operation; two occurred on the second and fourth days respectively.

The results in these cases indicate that by greatly increasing the volume of interstitial fluid by administration of isotonic sodium lactate, the circulatory collapse and reduc-

tion in plasma volume can be counteracted.

The emergency use of sodium lactate in burn shock seems justified. Further studies are needed to evaluate the possible added benefit of small amounts of plasma.

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* * *

Tinnitus Aurium: Observations on Its Nature and Control

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The hypothesis on which this investigation has been based is that tinnitus is the homologue in the auditory apparatus of paresthesia in the apparatus of common sensation. It represents a paresthesia of the cochlear nerve, and is evidence of an active disease process.

If this view is correct, tinnitus and its accompanying deafness should present a clinical picture comparable with that of peripheral neuropathy and should respond to the same general principles of treatment which have been found effective in that condition.

To test this view, some clinical experi-

ments have been made by interrupting the sympathetic pathway (stellate ganglion block, 18 cases) and by the exhibition of vasoconstrictor and vasodilator substances.

The results of these experiments will be described. They would seem to support the thesis. The results of treatment will also be described in a group of 175 patients observed over the years 1940-1943. Treatment was directed toward abolishing the assumed vascular disturbance with a vasodilator substance, nicotinic acid. Results for cases of all types show 15 per cent obtaining complete relief, 48 per cent definite improvement, a total of 63 per cent.

* * *

Accelerated Postpartum Involution of the Uterus with Vitamin B Complex Therapy

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MORTON S. BISKIND

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Observations that the liver loses its ability to inactivate estrogen in vitamin B complex deficiency, and that B complex restores this function,¹ were applied clinically to treatment of syndromes associated with excess estrogen (menorrhagia, metrorrhagia, cystic mastitis, premenstrual tension).² Among patients thus treated, one had men-

orrhagia several months postpartum associated with persistent uterine subinvolution and numerous indications of nutritional deficiency; the uterus involuted rapidly on B complex therapy. Two other patients with nutritional deficiency had a history of postpartum uterine subinvolution.²

On the assumption that the latter condition is related to excess estrogen, owing to failure of destruction in the liver, two groups of pregnant women—all private patients—were studied. One was maintained on an average diet; the other received substantial supplements of vitamin B complex during pregnancy. All the patients were examined 6 weeks postpartum for evidence of uterine subinvolution. In the control group of 107, 6 patients had poor involution; in 23 it was fair, in 78 good and in none could it be called excellent. In the group of 76 that received B complex, none had poor involution; in 3 involution was fair, in 56 good and in 17 excellent. Thus

the rate of involution was definitely enhanced in the group receiving B complex.

Recent reports emphasize the inadequacies of American diets during pregnancy. Peoples subsisting largely on whole grains customarily require shorter periods of postpartum rest than our own usual minimum of ten days. This study provides further evidence for the need of a greatly increased intake of vitamin B complex during pregnancy and the puerperium.

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* * *

The Effect of Vitamin A Supplements on the Concentration of Vitamin A in the Blood During Pregnancy

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In a previous communication¹ we have shown that during the last trimester of pregnancy there is a fall in the concentration of vitamin A in the blood whereas the carotene level is sustained. The decrease in the blood level of vitamin A is probably due to an increased demand by the fetus for this vitamin during the last 3 months of pregnancy. Analysis of the vitamin A content of the livers of 24 newborn infants has revealed considerable quantities of vitamin A.

The present study was undertaken to ascertain whether, by administering vitamin A supplements daily to pregnant women, the fall in vitamin A could be prevented during the last 3 months of pregnancy. Forty women enrolled in the Maternity Service of Beth Israel Hospital were given 10,000 units of vitamin A daily and blood levels for the vitamin were determined prior to the administration of vitamin A and, again, toward the end of pregnancy.

The results of this study revealed that the vitamin A blood level could be prevented, in most instances, from falling during the

last trimester by the administration of 10,000 units of vitamin A daily. In those women whose blood levels were low prior to the administration of vitamin A the concentration of vitamin A in the blood rose following the use of the vitamin supplement.

The vitamin A blood levels of the umbilical cords were also obtained in order to determine whether the administration of vitamin A supplements during pregnancy would raise the concentration of vitamin A in the blood of newborn infants. It was found that, despite these daily supplements, the vitamin A blood levels of the umbilical vessels were not appreciably increased. Furthermore, the administration of very large amounts of vitamin A during labor (200,000 units), brought about no increase in the vitamin A blood levels in the umbilical cord although the maternal blood values were considerably enhanced. These observations would indicate that the transmission of vitamin A through the placenta is quite limited. Similar studies with the use of carotene are now being carried out.

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* Captain, Medical Corps, Medical Department Research Laboratory, Edgewood Arsenal, Maryland.

Pedicle Patch-Graft Pyloroplasty

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A plastic operation is described consisting of the excision of the anterior wall of the pylorus, including the sphincter and adjacent portions of the stomach and duodenum, followed by repair of the resultant defect with a viable pedicle patch-graft taken from the greater curvature of the stomach and including all gastric layers. Fifteen dogs were operated upon, nine successfully.

The stomach x-rayed three weeks after this operation empties more quickly than

normal and sphincteric action by the antral (pre-pyloric) muscles is indicated.

The grafts showed satisfactory healing with no tendency toward ulceration, atrophy, out-pouching, or stenosis. The identity of the layers of the grafts was preserved histologically 3 weeks postoperatively. Those dogs which survived showed a satisfactory postoperative course over various periods of observation up to ten months.

* * *

*Studies on the Prevention and Treatment of Experimental Renal Obstruction from Sulfadiazine**

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Therapeutic measures most commonly employed and regarded as effective at the bedside in the prevention and treatment of renal obstruction caused by sulfadiazine, consist in the "forcing of fluids" in combination with massive alkalization. This investigation represents an attempt to evaluate the merits of these clinical measures under the standard conditions of the animal experiment. It contains, in addition, an approach to some new therapeutic procedures, not yet tested clinically, concerning the dislodgment of a fully established renal block caused by intratubular precipitation of sulfadiazine.

In the *Prevention* of renal obstruction, the following method was employed: Closely bred albino rats from our own standard colony were used in all experiments. Daily stomach tube feedings of fixed amounts of water represented the "forcing of fluid." Alkalization was obtained by adding sodium bicarbonate to the water. For the purpose of comparison, two subgroups received solutions containing an acidifying instead of an alkalinizing salt (sodium chloride and am-

monium chloride). After standard conditions had been established, sodium sulfadiazine was injected chronically into all rats, in amounts which were known to produce invariably massive precipitation of sulfadiazine in the renal tubules, provided no therapy was employed. Throughout the experimental period which varied from 3 weeks to 9 weeks in individual tests, volume, specific gravity, pH and drug concentration of the urine were recorded daily and frequent determinations of the sulfadiazine level and nonprotein nitrogen content of the blood were also carried out. Complete post mortem examinations were performed on all animals succumbing during the experiment and also on all survivors, which were killed by exsanguination. Important organs of representative animals were studied histologically.

Chronic sulfadiazine intoxication produces in rats the most significant pathologic-anatomical changes in the kidneys, in the aorta and other parts of the arterial tree and in the thyroid gland.

The striking success of alkalization in combination with the "forcing of fluids" was clearly borne out by the high rate of

* This investigation has been aided by a grant from the Josiah Macy, Jr., Foundation.

survival (no death), and the almost complete absence of significant pathological lesions in the alkali treated animals. The forcing of water alone, however, as well as the administration of acidifying salt solutions did not provide adequate protection. Animals of these groups succumbing to the sulfadiazine intoxication revealed, without exception, massive intratubular precipitation of sulfadiazine accompanied by severe tubular dilatation and degeneration of the kidneys. Apparently related to the renal impairment was the aortic damage which consisted in a necrosis of the media starting in the muscle fibers and followed by swelling and destruction of the elastic membranes and imbibition of the necrotic tissue with calcium salts. In many advanced instances the aorta assumed a bamboo-stick-like appearance, because of the segmental arrangement of bulging calcified rings, similar to the "goose's trachea" described in the medial sclerosis of Moenkeberg. True bony metaplasia developed in some cases of longer standing. The thyroid gland showed macroscopically marked increase in size and upon histological examination presented a picture of seemingly high glandular activity (as previously described by MacKenzie and MacKenzie and others).

The investigation proved that in the animal experiment intrarenal concrement formation from sulfadiazine and its serious consequences can be prevented by alkalization in conjunction with the "forcing of water."

In the *Treatment* of renal obstruction, standardized experimental conditions were established in the following manner: The renal block was produced in albino rats by intraperitoneal injection of a single fatal dose of sodium sulfadiazine. If left untreated the animals invariably developed pronounced and long-lasting renal obstruction from intratubular precipitate of sulfadiazine, and 80 per cent succumbed to this complication after 2-3 days. Treatment consisted in stomach tube feedings of fixed amounts of water or salt solutions (containing either NaHCO_3 , NH_4Cl , a mixture of these two, or NaCl). The fluids were given

twice daily, starting with the day of renal obstruction and continuing for at least one or several more days.

The most striking result was the excellent therapeutic success achieved with solutions of sodium chloride and of the mixture of NaHCO_3 and NH_4Cl . They made possible the complete recovery of all rats from an otherwise fatal sulfadiazine intoxication, whereas no benefits were derived from the "forcing of water" alone. The water-sodium bicarbonate combination even shortened the time of survival, and ammonium chloride, in addition to a further reduction of the life span, also increased the mortality to 100 per cent. Serum pH values obtained from heart blood indicated the presence of a severe uncompensated acidosis in the ammonium chloride group, and the development of an uncompensated alkalosis in the bicarbonate treated animals. The pH values of the other groups remained within the normal range.

From these findings the remarkable therapeutic effect of a mixture of ammonium chloride and sodium bicarbonate, in exactly the same concentrations, which when administered separately had only toxic effects, can now be explained. The combination of the alkalizing and acidifying salt in one solution will prevent dangerous changes in the acid-base balance of the body, which are so readily elicited in the presence of renal obstruction, and will thus enable the increased crystalloid concentration to initiate a powerful and life-saving diuresis (salt diuresis). This latter contention would also explain the therapeutic effect of large doses of saline solution despite its drawback of being a slightly acidifying agent.

The procedure employed in the latter investigation, represents a simple method for accurate comparative experiments on the treatment of renal obstruction from sulfadiazine.

Studies with modifications of composition, dosage and route of administration of therapeutic agents and with variations in the time of onset, frequency and duration of therapy are under way and will be reported at a later date.

*Psychological Changes in Late Post-Concussion Head Injuries**

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This is a partial report on the selection and use of tests for evaluating the relative operation of "neurotic," "diffuse organic" and "normal" mechanisms respectively responsible for the production of late post-concussional changes in dispositions and intellect following head injury. Personality and mental changes were chosen as the most promising late post-concussional complaints for investigation because they have not only a high frequency of occurrence but they are also capable of being objectively measured by psychological and psychophysiological techniques. The experimental procedure of empirical selection and careful matching of subjects in each of the three "pure" cultures or groups was used in preference to the more usual random sampling or selection technique. The method of working with "pure" subjects, well matched with reference to age, intelligence, sex, etc., provides more easily the clearcut differences in test responses needed for identifying the essential neurotic and organic mechanisms operating within the individual. The practical clinical use of the characteristic test responses thus discovered is to be in intra-individual diagnosis and not in merely determining group differences. The three experimental "pure" cultures, all of which were matched with reference to the afore-

mentioned factors, were: 1) normal subjects without psychoneurotic reactions or head injury of any kind, 2) patients with diffuse post-concussional brain damage without any psychoneurotic features who have adjusted well in their domestic and work responses even though at a lower level, and 3) patients with clear-cut psychoneurotic features without history of head injury.

These groups were studied with a preliminary battery of 33 promising psychological tests. Six of these were finally chosen. Each of these six tests provided a measurable positive response pattern characterizing each of the 3 groups mentioned above. Slides were presented to show the occurrence of test response patterns in the individual subjects making up each of these "pure" groups. The patterns were so characteristic as to differentiate each member of a group from a member of any of the other 2 groups. The normal pattern was found to apply to subjects of superior intelligence as well as to those within the range of the experimental subjects. The pattern indicating diffuse brain damage was also found to be entirely valid in those head-injured subjects who fell above or below the limitations of intelligence and age as required by the matching criteria. In order to exhibit its method of practical clinical application the battery was applied to the usual types of head-injured cases with a mixture of organic and neurotic features. They exhibited test patterns from which the relative weights of both of these features could be estimated.

* The work described in this abstract represents a partial report on research done under a contract (Head Injury Project No. OEMcmr.-148) recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University. This project is directed by Drs. Tracy J. Putnam and John G. Lynn.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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AUGUST 1944

JAUNDICE FOLLOWING
ADMINISTRATION OF HUMAN SERUM

Harvey Lecture, March 16, 1944

JOHN W. OLIPHANT

Surgeon, U.S.P.H.S.*

J JAUNDICE following administration of materials containing serum of the homologous species has been observed repeatedly both in man and in lower animals. It is still unknown whether this type of jaundice is identical with naturally occurring so-called infectious hepatitis.

One of the earliest reports of this condition is that of Hirsch¹ who records an outbreak in 1883-4 of jaundice among individuals vaccinated with "humanized lymph in glycerine." Among 1,289 persons vaccinated, 191 or 14.8 per cent developed jaundice after incubation periods "extended to several weeks and even to a couple of months." No cases developed among 500 persons vaccinated with a different lymph.

In 1918 Theiler² reported a condition known as "staggers" in horses, which followed administration of homologous serum. Jaundice was a marked sign. The incubation period varied from 27 to 165 days and the mortality varied from 4 to 18 per cent among large groups of immunized animals. Slagsvold³ found that 101, or 4.2 per cent of 2,400 horses treated with anti-anthrax serum developed liver damage from 8 to 95

* From the Division of Infectious Diseases, National Institute of Health, Bethesda, Maryland.

days following injection of the material. In most cases the elapsed period was 50 to 60 days. A similar condition in horses following the administration of equine encephalomyelitis vaccine containing homologous serum has been observed in this country.^{4, 5}

MacNalty⁶ drew attention to the occurrence of jaundice among 37 of 82 to 109 persons who had been given convalescent measles serum from the same pool of material. Seven deaths were recorded. Convalescent measles serum in doses of 4.5 cc. was given to seven children and in 75 to 83 days they all developed severe jaundice. Three cases terminated fatally. Two months later two children who had had contact with these patients developed mild infective hepatitis.⁷

Findlay and MacCallum⁸ found that hepatitis was a complicating factor in the use of yellow fever vaccines. Different types of vaccines used produced jaundice; the only common components in the products were human serum and the attenuated virus of yellow fever. During a five-year period 3,100 persons were immunized against yellow fever and 89, or 2.87 per cent, of these developed jaundice. The average incubation period was 2 to 3 months with a range of 36 days to 7 months. Hepatitis has been associated with the use of yellow fever vaccine by other workers. Soper and Smith⁹ described the first series of cases occurring in South America. A vaccine containing immune monkey serum and tissue culture virus was used. Among 244 persons immunized, 66, or 27 per cent, developed hepatitis. The incubation period was prolonged.

Fox and his coworkers¹⁰ studied two outbreaks of hepatitis following the use of yellow fever vaccine in Brazil. In 1939, 304 persons were immunized and 27 per cent suffered from hepatitis during the fourth and fifth months following immunization. In 1940, 35 lots of vaccine were used to vaccinate 107,169 persons. There were only 93 cases, or 0.1 per cent, of jaundice among 87,878 persons given material from 33 lots of vaccine. Two other lots produced a greater amount of jaundice among the recipients. The attack rate with one lot used among 9,604 individuals was 7.68 per cent and for another lot given to 9,587 persons the rate was 1.56 per cent. The average incubation period was 24.8 weeks for the 33 lots of vaccine, 17.8 weeks for the lot producing the highest attack rate of icterus, and 20.4 weeks for the other lot. A total of 25 deaths was recorded.

Recent U. S. Army experience with yellow fever vaccine resulted

in 28,585 cases of hepatitis with 62 deaths as of July 24, 1942.¹¹

Immunization against pappataci fever has also resulted in the appearance of jaundice after a prolonged period. The method used for immunization consisted of separate inoculations of virus and antiserum. The source of virus was human blood obtained during the acute stage of the disease. Sergiev *et al*,¹² studied 100 cases of jaundice resulting from the use of such materials. The incubation period varied from 63 to 146 days; about 50 per cent of the cases occurred between 85 and 95 days after inoculation. About 30 per cent of those vaccinated subsequently developed hepatitis.

A report of the British Ministry of Health¹³ attributes 48 cases of jaundice with 8 deaths to the use of pooled convalescent and adult human serum for measles. Incubation periods ranged from 16 to 161 days. Twelve cases of jaundice due to transfusion were also recorded. A number of other cases of hepatitis developed following the use of mumps convalescent serum. The writers conclude that, "any doubt as to the reality of the association is removed by the frequency with which hepatitis has followed the injection of human blood products."

In addition to the reports of jaundice secondary to immune sera and supposedly normal serum, there were in 1943 two reports of jaundice following the administration of pooled human plasma, reconstituted dried human serum and blood transfusion. Beeson¹⁴ in this country reported seven cases. Of these, four had received one or more transfusions of citrated blood only. The other three persons had received both pooled plasma and citrated blood at different times. In five of the cases the minimum possible incubation period varied from 69 to 111 days. In England, Morgan and Williamson¹⁵ saw nine cases which developed following transfusion with serum, plasma or both. The incubation periods varied from 7 to 16 weeks.

Findlay and Martin¹⁶ present evidence that an "infective icterogenic agent" is present in the nasopharynx of individuals developing hepatitis following administration of yellow fever vaccine. While some doubt might be maintained concerning two of the cases produced by this experimental approach, the evidence in the third case (Case 2) seems convincing. Voegt¹⁷ attempted to transmit the agent of infective hepatitis from one person to another with results which are suggestive.

Lainer¹⁸ carried out a human inoculation experiment in which he inoculated healthy persons with blood or duodenal juice from patients

three to ten days after the appearance of jaundice. The duodenal juice was introduced into the duodenum by tube and blood was given by transfusion. The study was stated to be entirely negative; duration of observation was not given.

The relation between jaundice following administration of homologous serum and the disease known as infectious hepatitis or epidemic catarrhal jaundice is not known. According to the work of Cullinan,¹⁹ Pickles,²⁰ and others, infectious hepatitis is spread by droplet infection and has an incubation period varying from 20 to 40 days. Two epidemics, one in Canada, the other in Sweden, reported by Fraser²¹ and Hallgren²² appear to have been due to contamination of drinking water by sewage; transmission by the respiratory tract was not seen. Very few secondary cases have been attributed to association with cases of jaundice following the administration of homologous serum. This disease is further peculiar in that the incubation period is prolonged considerably over that of infectious hepatitis.

Many attempts to isolate the causative agent of infectious hepatitis and serum-induced jaundice have been made, so far without success. It is generally supposed that it is a virus.

Isolation of an etiologic virus was claimed by Siede and Meding²³ who inoculated the chorioallantois of chick embryos with duodenal juice obtained from a jaundiced patient. Proof of isolation consisted only in the ability of their material to kill the chick embryos in 4-5 days. The lethal agent was lost on the fourth transfer.

An opportunity to study an epidemic of jaundice following the use of yellow fever vaccine presented itself when an outbreak occurred in the Virgin Islands in the summer of 1942. Sufficient epidemiological evidence²⁴ was accumulated to establish the identity of the disease and material was obtained for study. Since August 1942 a human inoculation study has been carried on in an effort to gain further information concerning the nature and etiology of this condition.

EPIDEMIOLOGY

During 1942 a total of 11,358 individuals on the islands of St. Thomas and St. John, Virgin Islands, was inoculated with lot 331 yellow fever vaccine containing pooled human serum. According to reliable data there were 11,265 persons living on the island of St. Thomas and 765 on the island of St. John, but owing to wartime increases in

TABLE I

DATES OF IMMUNIZATION AND NUMBERS OF PERSONS VACCINATED
WITH YELLOW FEVER VACCINE IN THE VIRGIN ISLANDS

| <i>Date immunized, 1942</i> | <i>Place</i> | <i>Num- ber immu- nized</i> | <i>Date immunized, 1942</i> | <i>Place</i> | <i>Num- ber immu- nized</i> |
|-------------------------------------|--------------|---|-------------------------------------|--------------|---|
| Mar. 4..... | St. Thomas | 490 | Mar. 16..... | St. Thomas | 1,554 |
| Mar. 5..... | do | 403 | Mar. 18..... | do | 1,505 |
| Mar. 6..... | do | 624 | Mar. 20..... | do | 2,568 |
| Mar. 9..... | do | 1,134 | Mar. 23..... | do | 298 |
| Mar. 10..... | do | 392 | Mar. 28..... | do | 410 |
| Mar. 11..... | do | 596 | Apr. 17..... | St. John | 211 |
| Mar. 12..... | do | 597 | | | |
| Mar. 13..... | do | 576 | Total..... | | 11,358 |

population these figures may be too low. There were 11,147 persons vaccinated with yellow fever vaccine on St. Thomas between March 4 and March 28, 1942, and 211 persons vaccinated on St. John on April 17, 1942. The same lot of vaccine was used throughout the immunization procedure. The dates of vaccination together with the numbers of persons vaccinated are given in Table I.

Jaundice was first noted in May, and by June 2, 1942, about 50 cases had been observed. During the next two weeks it was estimated that between 300 and 500 cases occurred. In order to obtain some exact knowledge concerning the incidence of the disease following the administration of vaccine, a survey was done in the city of Charlotte Amalie, St. Thomas, between July 6 and July 16. A group of 1,198 persons was studied. This sample is roughly 10 per cent of the population involved. The data obtained from this survey are included in Table II. It was established that 14.7 per cent of the vaccinated individuals developed symptoms of hepatitis following vaccination and that the incidence was greatest in the age groups between 20 and 59 years. Among 159 persons who were said not to have been vaccinated, 3 cases occurred. Inasmuch as the vaccination records were not entirely adequate it is somewhat difficult to assess the significance of these cases.

Conditions were not suitable for accurate determination of the incubation period. Among a group of 75 patients from whom reliable and

TABLE II

SAMPLE SURVEY OF CHARLOTTE AMALIE, VIRGIN ISLANDS, SHOWING INCIDENCE OF JAUNDICE FOLLOWING YELLOW FEVER IMMUNIZATION

| Age | Vaccinated population | | | Unvaccinated Population | | | Total | | |
|---------|-----------------------|------------------------------|-------------------------|-------------------------|------------------------------|-------------------------|-----------------|------------------------------|-------------------------|
| | Number Surveyed | Number of cases of hepatitis | Per cent with hepatitis | Number Surveyed | Number of cases of hepatitis | Per cent with hepatitis | Number Surveyed | Number of cases of hepatitis | Per cent with hepatitis |
| Under 1 | 31 | 0 | 7.5 | 17 | | | 297 | 20 | 6.7 |
| 1-4 | 127 | 11 | | 13 | | | | | |
| 5-9 | 107 | 9 | | 2 | | | | | |
| 10-14 | 120 | 16 | 11.8 | 3 | | | 260 | 29 | 11.3 |
| 15-19 | 125 | 13 | | 12 | | | | | |
| 20-24 | 119 | 19 | 18.8 | 16 | | | 236 | 40 | 16.9 |
| 25-29 | 88 | 20 | | 13 | 1 | | | | |
| 30-34 | 76 | 20 | 21.1 | 11 | | | 153 | 28 | 18.3 |
| 35-39 | 57 | 8 | | 9 | | | | | |
| 40-44 | 45 | 8 | 22.8 | 6 | | | 77 | 16 | 20.8 |
| 45-49 | 25 | 8 | | 1 | | | | | |
| 50-54 | 48 | 9 | 21.4 | 4 | | | 85 | 15 | 17.7 |
| 55-59 | 22 | 6 | | 11 | | | | | |
| 60-64 | 18 | 2 | 12.2 | 13 | 1† | | 90 | 8 | 8.9 |
| 65-69 | 19 | 2 | | 10 | | | | | |
| 70+ | 12 | 2 | | 18 | 1 | | | | |
| | 1,039 | 153* | 14.7 | 159 | 3 | 1.9 | 1,198 | 156 | 13.0 |

* Including 12 cases with all signs and symptoms except icterus.

† 1 case with all signs and symptoms except icterus.

observed data could be elicited the average period between immunization and development of hepatitis was 103 days with a range of 75 to 130 days.

The disease was similar to that noted by other observers. Clinically, the disease varied considerably from very mild to extremely severe cases. Onset usually began with headache, pains in the shoulders and back, and frequently with pains in the fingers. A sensation of fullness in the epigastrium was quite characteristic and with this was associated anorexia and nausea. Weakness was a common complaint. Within a day or so the urine was noted to be very dark and within 2 to 3 days icterus of the sclerae appeared. Constipation and clay-colored stools were noted

TABLE III

DATA CONCERNING VIRGIN ISLANDS SERUMS USED
IN POOL FOR EXPERIMENTAL GROUPS 2 AND 6

| Num- ber | Date vacci- nated, 1942 | Date jaun- diced, 1942 | Date bled, 1942 | Results of quan- titative van den Bergh test | Remarks |
|-------------|----------------------------------|---------------------------------|-----------------------|---|---------------------------|
| | | | | (mg. per 100 cc.) | |
| 6 | Mar. 4 | June 22 | July 6 | 0.68 | |
| 11 | Mar. 16 | June 28 | do | 1.07 | |
| 30 | Mar. 4 | | July 8 | 0.62 | |
| 40 | Mar. 20 | | do | 0.56 | |
| 43 | Mar. 6 | | do | 1.16 | |
| 47 | Mar. 6 | July 7 | do | 0.84 | |
| 49 | Mar. 4 | | do | 0.14 | Later developed jaundice. |
| 52 | Mar. ? | June 18 | do | ... | Icteric. |
| SJA | Apr. 17 | July 14 | July 17 | ... | do |

during the period of jaundice. Vomiting also occurred and varied considerably in severity. Usually vomiting was limited to one or two episodes but in a few instances was persistent, leading to marked dehydration.

There were cases which presented only dark urine, anorexia, vomiting, headache, and pains with no frank jaundice, while other cases remained jaundiced for at least a month. The average individual was jaundiced for about 6 to 10 days. The degree of illness did not appear to be closely associated with the duration of icterus as many who were jaundiced for a considerable period were ambulatory throughout the illness, while some who were jaundiced only a few days were bedridden during the period.

It seems evident from the standpoint of the previous history of immunization, the prolonged incubation period, and clinical symptoms that the disease under observation was identical with that previously described and designated as homologous serum jaundice.

Under the conditions of the outbreak it was deemed wise to limit our collection of possible infectious material to blood or serum which

TABLE IV
SUMMARY OF GROUPS INOCULATED SHOWING
INCIDENCE OF JAUNDICE

| Group | No. in Group | Inoculum | Cases of jaundice | |
|-------|--------------|--|-------------------|----------|
| | | | Number | Per cent |
| 1 | 50 | Group 1. Lot 331. Yellow fever vaccine in recommended dose. This vaccine contained pooled human serum and is of the same lot which produced jaundice in the United States Army and in the Virgin Islands. | 12 | 24 |
| 2 | 10 | Group 2. Pooled serum collected from nine individuals in the Virgin Islands who had received Lot 331 vaccine. Serum was diluted 1:5. Dose 0.5 ml. S.C.* See Table III. | 2 | 20 |
| 3 | 10 | Group 3. Lot 367. Dried yellow fever vaccine containing human serum. Heated in 56° C. water bath for 30 minutes before dilution. Given in recommended dose. | 2 | 20 |
| 4 | 10 | Group 4. Pooled weekly specimens of serum from a mild case of jaundice in Group 1. Serum dilution 1:3. Dose 0.5 ml. S.C. | 0 | 0 |
| 5 | 10 | Group 5. Pooled weekly specimens of serum from a mild case of jaundice in Group 2. Serum dilution 1:3. Dose 0.5 ml. S.C. | 0 | 0 |
| 6 | 20 | Group 6. Pool of same specimens used in Group 2. Serum dilution 1:3. Dose 0.5 ml. S.C. See Table III. | 6 | 30 |
| 7 | 20 | Group 7. Pooled weekly serum specimens from a severely jaundiced patient in Group 1. Dilution 1:3. Dose 0.5 ml. S.C. | 3 | 15 |
| 8 | 20 | Group 8. Pooled weekly serum specimens from a moderately jaundiced patient in Group 1. Dilution 1:3. Dose 0.5 ml. S.C. | 1 | 5 |
| 9 | 10 | Lot 367. Yellow fever vaccine diluted as recommended and heavily irradiated with ultra-violet light, 1 hour at 2650 Å. and 1½ hours at 2537 Å. | 0 | 0 |
| 10 | 14 | Pooled weekly serum specimens taken before appearance of jaundice from patient in Group 1. Serum dilution 1:3. Dose 0.5 ml. S.C. | 4 | 28.7 |
| 11 | 15 | Group 11. Single serum specimen from same individual contributing to Group 10. Specimen taken about 2½ months after jaundice had subsided. Serum dilution same as in Group 10. Dilution 1:3. Dose 0.5 ml. S.C. | 0 | 0 |
| 12 | 10 | L. J. Serum. Had contributed serum to pool used in icterogenic vaccine. Had history of jaundice 1 year previously. Dose 0.5 ml. 1:4 S.C. | 0 | 0 |
| 13 | 10 | M. B. Serum. Description for Group 12. Serum applies here also. Dose 0.5 ml. 1:4 S.C. | 0 | 0 |

(Continued on p. 437)

TABLE IV—(Continued)

| Group | No. in Group | Inoculum | Cases of jaundice | |
|-------|--------------|--|-------------------|----------|
| | | | Number | Per cent |
| 14 | 11 | #38 pooled weekly serum specimens taken during pre-icteric period. Irradiated 45 min., 85% 2537 A. Dose 0.5 ml. 1 : 3 S.C. | 0 | 0 |
| 15 | 13 | Same serum used in Group 14, <i>non</i> irradiated. Dose 0.5 ml. 1 : 3 S.C. | 2 | 15.4 |
| 16 | 15 | Pooled dried plasma. One donor developed jaundice 4 days after bleeding. Dose 1 ml. S.C. | 0 | 0 |
| 17 | 10 | Serum from young man during spontaneously occurring jaundice. Dose 1 ml. 1 : 4 S.C. | 4 | 40 |
| 18 | 3 | Same serum used in Group 17. Dose 1 ml. 1 : 4 I.N.† | 0 | 0 |
| 19 | 3 | #38 pooled pre-jaundice phase serum. Dose 1 ml. 1 : 4 I.N. | 0 | 0 |
| 20 | 20 | #125 pooled pre-jaundice serum irradiated in thin quartz cell 2½ sec. by high energy low pressure water-cooled mercury vapor lamp. Dose 1 ml. 1 : 4 S.C. | 0 | 0 |
| 21 | 9 | Same serum as in Group 20 <i>non</i> irradiated. Dose 1 ml. 1 : 4 S.C. | 1 | 11 |
| Total | 273 | | 37 | |

* S.C.—Subcutaneously.

† I.N.—Intranasally.

could be shipped under suitable conditions. Many samples were taken and from these nine were selected for experimental use. These are tabulated in Table III.

EXPERIMENTAL STUDY

Volunteers were obtained in an institution with a population of about 1700. During the greater part of the study it was possible to use groups composed equally of both sexes. After 189 persons had been inoculated and 30 had developed jaundice it was found there was no apparent difference in susceptibility of the sexes and thereafter either sex available was used. Individuals with infectious diseases or history of recent antisyphilitic treatment were excluded. The age range was 13-57.

Table IV shows the size of groups used with brief descriptions of materials used for inoculation, and tabulation of cases of jaundice. Groups are arranged in chronological order in the table.

Each serum given was diluted with phosphate-buffered normal saline solution, pH 7.6, Berkefeld-N-filtered and cultured for sterility. Subcutaneous inoculation was always into the arm. Intranasal inoculation was done with the subject lying on the back of a table with the head dependent. Half the inoculum was dropped into each nostril and the subject then sniffed the material well back into the nose. Materials used for inoculation including sera and dried vaccines were stored routinely at 4° C. for variable periods up to a year. The maximum survival time of the icterogenic agent at this temperature was not determined.

All persons inoculated were bled just before inoculation and weekly afterward for 4 to 6 months. Bleeding was done on the same day of the week for each person and at about the same time of day, usually 3-5 hours after breakfast. The serum was separated the same day and a quantitative indirect Van den Bergh estimation was done.²⁵ Readings were made in a comparator using cobaltous sulfate standards.

Total leukocyte and differential counts were done weekly on the first few groups. No significant variation during the period of jaundice was seen in either count. Schilling counts were then done routinely each week and these failed to show any variation in jaundiced patients.

Moss blood grouping was done for each subject. No correlation between blood group and susceptibility to jaundice was found. Eighty-five sera were tested for Rh factor. Both Rh-positive and Rh-negative individuals were found susceptible to jaundice.

Some groups were skin tested just before inoculation with sera, one of which (Group 17) was icterogenic; 0.1 cc. of serum was given intracutaneously and the test was read 30 minutes later. Some slight reactions with small wheals up to 0.8 cm. in diameter with surrounding zones of erythema were seen. However, there was no correlation between the result of the skin test and susceptibility to jaundice, those subjects developing jaundice being equally divided, two showing small reactions and the other two no reaction. Non-icterogenic sera were also found to give similar slight reactions in some individuals.

The cephalin-cholesterol flocculation test of Hanger²⁶ was done weekly on each serum specimen, always with fresh serum on the day of bleeding. Invariably the test is strongly positive when clinical jaundice is present. In the subclinical range in our experience, the test may or may not be strongly positive. Many +, ++ and +++ reactions have been seen with sera from individuals who were in normal health so far

TABLE V

SUMMARY OF ALL EXPERIMENTAL GROUPS DEVELOPING
JAUNDICE SHOWING INCIDENCE ACCORDING TO AGE GROUP

| | <i>Inoculated</i> | <i>Developed jaundice</i> | <i>% developed jaundice</i> |
|-----------------|-------------------|-------------------------------|---------------------------------|
| 10 - 14 | 2 | 0 | 0.0 |
| 15 - 19 | 35 | 3 | 8.6 |
| 20 - 24 | 45 | 10 | 22.2 |
| 25 - 29 | 25 | 4 | 16.0 |
| 30 - 34 | 27 | 8 | 29.6 |
| 35 - 39 | 17 | 4 | 23.5 |
| 40 - 44 | 13 | 3 | 23.0 |
| 45 - 49 | 9 | 3 | 33.3 |
| 50 - 54 | 2 | 2 | 100.0 |
| 55 - 59 | 1 | 0 | 0.0 |
| Total | 176 | 37 | |

as known. Difco antigen was used.

Icteric serum specimens have been repeatedly examined in the electron microscope by Lt. Don R. Mathieson of the Naval Research Medical Center. No particles of uniform morphology were found.

In Table V are listed all experimental groups in which cases of jaundice developed, according to age groups. The size of the groups is too small to give an accurate idea of the true susceptibility. The survey done in the Virgin Islands is undoubtedly much more reliable in this respect because of the larger number involved.

For statistical purposes jaundice was considered to be present when the serum bilirubin value was 1.0 mg. per cent or higher. Clinical jaundice was usually not seen until this value was 2.0 mg. per cent or more. In Table VI are listed all cases of jaundice occurring in experimental groups with data obtained from weekly blood specimens of each individual. In a few cases subjects were removed from the institution before complete disappearance of jaundice. A short statistical summary of 37 cases of jaundice is given in Table VII. Incubation period is here defined as elapsed time in weeks between inoculation and first appearance of a serum bilirubin of 1.0 mg. per cent or more. Duration of jaundice here

TABLE VI
OBSERVED DATA, CASES OF JAUNDICE ONLY

| <i>Group</i> | <i>No.</i> | <i>Age</i> | <i>Incubation period, wks.*</i> | <i>Duration of jaundice, wks.†</i> | <i>Time re- quired for serum bilirubin to return to 0.5 mg. %, wks.</i> | <i>Highest serum bilirubin observed, mg. %</i> |
|--------------|------------|------------|---|--|---|--|
| 1 | 2 | 17 | 14 | 1 | 3 | 5.0 |
| 1 | 7 | 15 | 13 | 2 | 3 | 3.0 |
| 1 | 8 | 24 | 16 | 2 | 3 | 1.1 |
| 1 | 12 | 22 | 14 | 1 | 2 | 1.0 |
| 1 | 13 | 33 | 13 | 3 | 4 | 10.0 |
| 1 | 23 | 46 | 16 | 3 | 3+ | 8.0 |
| 1 | 30 | 28 | 12 | 3 | 5 | 4.5 |
| 1 | 31 | 21 | 5 | 1 | 2 | 1.7 |
| 1 | 33 | 21 | 12 | 2 | 3 | 4.0 |
| 1 | 38 | 38 | 14 | 6+ | 6+ | 20.0 |
| 1 | 44 | 32 | 12 | 1 | 2 | 3.0 |
| 1 | 48 | 47 | 13 | 4 | 5 | 9.0 |
| 2 | 57 | 33 | 15 | 1 | 2 | 1.2 |
| 2 | 59 | 26 | 10 | 2 | 4 | 2.2 |
| 3 | 61 | 42 | 19 | 7+ | 7+ | 16.0 |
| 3 | 70 | 37 | 18 | 2 | 3 | 2.8 |
| 6 | 132 | 36 | 12 | 1 | 1 | 2.1 |
| 6 | 136 | 39 | 12 | 1 | 1 | 2.0 |
| 6 | 138 | 22 | 11 | 3 | 3 | 5.6 |
| 6 | 162 | 31 | 12 | 2 | 3 | 1.2 |
| 6 | 163 | 21 | 12 | 3 | 3+ | 2.6 |
| 6 | 167 | 24 | 10 | 2 | 3 | 4.8 |
| 7 | 150 | 33 | 8 | 2 | 4 | 5.6 |
| 7 | 176 | 21 | 10 | 1 | 2 | 2.8 |
| 7 | 179 | 40 | 10 | 4 | 6+ | 2.6 |
| 8 | 188 | 32 | 17 | 2 | 3 | 4.8 |
| 10 | 201 | 24 | 13 | 2 | 2 | 2.4 |
| 10 | 208 | 19 | 8 | 1 | 2 | 3.2 |
| 10 | 217 | 26 | 9 | 2 | 4 | 2.4 |
| 10 | 220 | 22 | 10 | 3 | 4 | 8.0 |
| 15 | 112 | 28 | 14 | 3 | 4 | 3.3 |
| 15 | 125 | 43 | 9 | 3 | 4 | 5.4 |
| 17 | 266 | 31 | 20 | 1 | 1 | 2.1 |
| 17 | 271 | 51 | 19 | 3 | 4 | 6.2 |
| 17 | 272 | 46 | 16 | 4 | 5 | 10.0 |
| 17 | 273 | 52 | 20 | 1 | 2 | 2.1 |
| 21 | 306 | 30 | 10 | 2 | 4 | 2.4 |

* Elapsed time until serum bilirubin value of 1.0 mg. % or higher is found.

† Time during which serum bilirubin of 1.0 mg. % or more is found.

TABLE VII
STATISTICAL SUMMARY OF CASES OF JAUNDICE

| | <i>Range</i> | <i>Average</i> | <i>Median</i> | <i>Mode</i> |
|---|--------------|----------------|---------------|-------------|
| Incubation, period, weeks..... | 5 - 20 | 12.9 | 12 | 12 |
| Serum bilirubin, mg. % (maximum observed) | 1.0 - 20.0 | 4.7 | 3.0 | |
| Duration of jaundice, weeks*..... | 1 - 7 | 2.35 | 2 | 2 |
| Serum bilirubin elevated, weeks†.... | 1 - 7 | 3.3 | 3 | 3 |

* Number of weeks during which serum bilirubin value was 1.0 mg. % or higher.

† Number of weeks required for serum bilirubin to return to 0.5 mg. % or less.

means the time in weeks during which the serum bilirubin remained at 1.0 mg. per cent or higher.

In two cases of jaundice a biphasic rise in serum bilirubin was seen. Both cases occurred in group 1. In one case the first rise occurred after 3 weeks and reached 1.1 mg. per cent. In the thirteenth week a second rise to 3.2 mg. occurred with a further rise to 10.0 mg. the following week. In the other case the first rise occurred after 5 weeks reaching 1.8 mg. in the eighth week with a secondary rise to 1.7 mg. in the fourteenth week.

Clinically most cases were quite mild; epigastric discomfort and nausea were commonly present shortly before jaundice appeared. Vomiting occurred in a few cases. Clay-colored stools and dark urine were present during jaundice. Slight fever up to 100°-101° F. was noted in a few cases at about the time of onset. Anorexia was usually present during jaundice. Most jaundiced patients remained ambulatory. Dermatitis and arthritis were not seen.

So far as known no contact cases of jaundice occurred. Only 3 cases have appeared among 1,400 uninoculated individuals not included in this study during the past 18 months in the institution's population of about 1,700. One of these spontaneous cases was found to have carcinoma of the liver. During one period of 4 months 40 uninoculated persons having close contact with the inoculated group in which jaundice was occurring were bled weekly and no evidence of jaundice was found among them.

Colonel Stanhope Bayne-Jones supplied sera from three persons who

had acted as donors to pools of serum used in preparation of batches of yellow fever vaccine which had produced jaundice in the United States Army during 1942. It was subsequently found that all three of these persons had histories of jaundice occurring several months before they were bled for the vaccine. Two of these sera were used for inoculation in groups 12 and 13. No cases of jaundice appeared in these groups.

The plasma used in group 16 was a part of one lot prepared commercially. Before the lot was released it was learned that one of the donors to the pool had developed jaundice a few days after being bled. The whole lot was immediately confiscated. On July 22, 1943 a group of 15 were inoculated with 1 cc. each of this material subcutaneously. No cases of jaundice developed. On December 10, 1943, another group of 10 were inoculated with the same material in a dose of 10 cc. intravenously. To date no jaundice has appeared in the second group.

The serum used for inoculation in group 17 was obtained from a boy 18 years old, an inmate of the institution, who developed jaundice spontaneously. He had had no known contact with members of the experimentally inoculated groups. Serum was obtained from him five days after jaundice had appeared, at which time he complained only of poor appetite; there was no fever, the serum bilirubin value was 12 mg. per cent; the Hanger reaction was strongly positive. This case and the 4 cases which subsequently developed in those inoculated from it were indistinguishable in appearance from the other cases seen. The incubation periods ranged from 16 to 20 weeks.

Reports of two cases of jaundice among the personnel of one Coast Guard vessel were received in 1943. Both men were vaccinated the same day with one lot of "aqueous base" yellow fever vaccine containing no serum. One developed jaundice in forty-nine days, the other in 129 days. The findings in both cases, as reported, were consistent with the finding in cases of our series. On November 11, 1943, thirteen subjects were inoculated with twice the recommended dose of the same lot of vaccine mentioned above as used on the Coast Guard vessel. To date no cases of jaundice have developed in this group.

Attempts were made to transmit jaundice to animals, using materials which had produced the disease in humans. These included yellow fever vaccine as well as sera derived from patients in the Virgin Islands and from persons with experimentally produced jaundice. Monkeys, pigs,

rabbits, guinea pigs, white rats, Swiss mice, cotton rats and Syrian hamsters were employed. In no instance were we able to produce any illness in experimental animals which could not be accounted for by other agents and no animals became jaundiced as determined by physical or chemical examinations.

E. W. Goodpasture supplied specimens of liver from fatal cases of jaundice which occurred following the use of yellow fever vaccines. Extracts of these specimens were made both with 95 per cent alcohol and normal saline solution. The extracts were used as antigens in complement fixation tests designed to determine whether or not serum antibodies were present following this type of hepatitis. In a limited series of tests negative results were obtained. Attempts were also made to produce a complement-fixing antigen in the developing chick embryo; these were inoculated both in the allantoic sac and the yolk sac. Embryos 9-10 days old were inoculated with icterogenic yellow fever vaccine. Serial transfers were made in both series at intervals of 3-4 days and at 1 week. No fixation resulted with allantoic fluid or yolk sac emulsions tested against human sera obtained after recovery from jaundice.

COMMENT

It was recognized in 1942 during an epidemic of jaundice in the United States Army that some agent in human serum employed as a diluent in yellow fever vaccine was probably responsible. The yellow fever vaccine now in use does not contain serum. The two cases described above of jaundice in personnel of the Coast Guard following administration of serum-free vaccine may well have been due to other causes than the vaccine and probably should be so regarded unless evidence to the contrary is obtained.

It is difficult to evaluate the claim of Findlay and Martin¹⁶ to have produced jaundice in 3 of 4 subjects inoculated with nasal washings of patients in the early stages of post-yellow fever vaccine jaundice. Two of these cases are claimed to have been subclinical jaundice. In one, T.P., the icteric index did not exceed 8 units. In the other, M.M., the only direct evidence of jaundice was a weakly positive direct reaction (serum Van den Bergh). So far as known no cases occurred among familial contacts of thousands of cases of jaundice occurring in the U. S. Army and it is felt that additional evidence should be obtained before concluding that the condition may be transmitted by the respiratory tract.

Since jaundice has repeatedly followed the administration of whole blood or blood products there is an urgent need for some means of detecting the presence of the jaundice-producing agent in the blood, or for some practical method for treating blood products so that the danger of jaundice following their use may be eliminated.

SUMMARY

Results of a sample survey of an epidemic of jaundice occurring subsequent to vaccination against yellow fever in the Virgin Islands in 1942 are given.

Jaundice was produced experimentally: 1. By the inoculation of two lots of yellow fever vaccine containing human serum. 2. By the inoculation of small amounts of filtered serum from each of three individuals and of a serum pool from nine individuals all of whom had previously received yellow fever vaccine containing human serum. 3. By inoculation of serum from one individual who had early spontaneously occurring jaundice.

Two sera which were icterogenic when inoculated subcutaneously failed to produce jaundice by the intranasal route.

Both sexes are apparently equally susceptible to this type of jaundice. Those of all four Moss blood groups and both Rh-positive and Rh-negative persons were found to be susceptible.

Susceptible persons did not give uniform local skin reactions to icterogenic sera.

The jaundice-producing agent is filterable, survives drying in vacuum, storage for long periods in serum at 4° C. and heating to 56° C. for one-half hour in the dried state. The agent was found to be present in the blood during the pre-jaundice period but not 2 ½ months after the disappearance of jaundice.

The icterogenic agent is apparently inactivated by short exposure to ultraviolet irradiation.

Transmission of jaundice by ordinary contact apparently did not occur during this experiment.

Attempts to produce jaundice in experimental animals were unsuccessful.

Antigens prepared from human livers and from chick embryos failed to fix complement in the presence of sera obtained after recovery from jaundice.

Attempts to visualize virus particles in icterogenic sera by electron microscopy were unsuccessful.

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MAJOR THERAPEUTIC TRENDS IN
AMERICAN PSYCHIATRY*

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IN THIS year of titanic struggle, the attention and effort of all are engaged in the greatest argument which has ever agitated the human race. The central issue in dispute is concerned fundamentally with forms of social organization, and differing attitudes as to what is humanly tolerable in the coercion of one group by another. The overreaching aggression of certain nations has ultimately mobilized against them the united sentiments and the massed forces of the rest of the world in bitter combat, bloodshed and devastation. In a world aflame with passionate strife, a small handful of us are gathered here this evening to consider together briefly a certain portion of the healing art, psychiatry, and to scan in a quick review the changes wrought in this art, and in its fundamental scientific concepts, by a century of effort on the part of our American predecessors and contemporaries. My assignment in this program is to discuss the major therapeutic trends.

Surely, it would seem, there could be no greater contrast than that between the most bitter war in history and the gentleness of a healing art devoted to the relief of the distraught mind. A decent respect for historical truth compels me to admit, however, that the record of this gentle art has been often punctuated by disputes of amazing bitterness and rancor. This unpleasant fact was brought to my mind with special force a few years ago, at a psychiatric convention. I met by chance in the lobby at the same moment two friends of mine, both eminent and successful psychiatrists, and one of them refused to shake hands or to speak with the other because of an enmity which had arisen over a difference of belief as to psychotherapeutic principles. Differing attitudes regarding proper principles of exercising therapeutic influence have a great power to arouse antagonism. This fact has had

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a crucial influence in determining therapeutic trends in psychiatry.

In the early decades of the 19th century when American psychiatry began, it took on social form and institutional substance as a humanitarian movement, motivated by kind sentiments, as expressed, for example, in the terms "Retreat" and "Asylum." The leading idea was not primarily that of therapy, but of care; nevertheless the responsibilities were entrusted to physicians and this fact made it inevitable that therapeutic impulses would have a large influence. Indeed Pinel's courage and success in trying out "moral management" had set a brilliant and encouraging therapeutic challenge in closest alignment with the humanitarian motives.

In my judgment the most useful brief review of major therapeutic trends in American psychiatry should concern itself primarily with psychotherapeutic orientations. In making the choice to emphasize the psychotherapeutic side of psychiatric work I am aware that one invites some of the unpleasant emotional reactions which seem always to have troubled the earnest discussion of this topic, yet I deliberately make this choice because it seems to me that the study of the psychotherapeutic trends provides the most penetrating glimpses into the general philosophy and therapeutic aims of the different psychiatric workers and different periods.

As the introductory scene in this review let us consider a few events in the two year period 1875 and 76, not because that was the historical beginning, but because certain dramatic events of that period give a useful cue to a fundamental theme for this brief essay.

A story is told regarding George M. Beard's paper before the American Neurological Association at its second annual meeting in 1876. Beard discussed the power of suggestion in the production and relief of symptoms. In the heated avalanche of contrary opinion which followed, William A. Hammond, who has been called the father of American neurology, is said to have stated angrily that if Beard's doctrine of psychological influence were accepted he would feel like throwing away his medical diploma and joining the theologians! This contemptuous rejection probably expressed quite well the attitude of the medical profession at that time toward psychotherapeutic methods.

This incident was approximately contemporaneous with the publication (in 1875) of the first edition of Mary Baker Eddy's *Science and Health*, to be followed in a few years by the appearance of the *Journal*

of *Christian Science*. It is interesting to note that Pierre Janet, in his extensive treatise on *Psychological Healing* gave greater emphasis and more space to Mary Baker Eddy than to any other American.

While acknowledging that the degree of institutional success of the Christian Science movement was phenomenal, the urge toward the development of its doctrines is not difficult to appreciate. Clinical experience shows us repeatedly how the recovered patient tends to over-generalize the principles which have helped him regain health. Thus, Mary Baker Eddy, after the cure of her hysterical paralysis by Phineas Quimby, formulated her therapeutic gospel in a religious form since that was the only extensive ideology available to her for large-scale philosophizing. The phenomenal growth of the Christian Science movement as a religion constituted an indirect indication, however, of the culpable neglect of psychotherapy by the medical men of that period; and then, in turn, the overdrawn tenets of the Christian Scientists and the disastrous neglect of elementary medical considerations by the healers of that cult certainly antagonized the medical profession and made even more difficult the sane and rational development of psychotherapeutic study as a part of the medical art.

In 1875, the year before Beard's paper, we may note the first exposition of Weir Mitchell's "rest cure," in Seguin's Series of American Clinical Lectures. Weir Mitchell's "rest cure" would now be considered by all as having been essentially a psychotherapeutic method, whose efficacy depended more on its unavowed psychological features than on its direct effects on "Fat and Blood," as Mitchell himself claimed. It seems probable to me that this excessively somatic mode of rationalizing his therapy reflected also the prevailing antagonism against psychological healing, just as did Beard's experience, but in the opposite sense. That is to say, Mitchell, being emotionally well attuned to the prevailing attitudes of medical leadership, was inclined automatically to steer away from the psychotherapeutic principles, whose borders he was skirting, and to formulate his undoubtedly successful experiences in the more acceptable somatic ideology. Mitchell may have understood that in addressing his medical colleagues he had to express himself in an idiom acceptable to medical prejudices. Here is a consideration worth the careful attention of anyone who would seek to understand the psychiatric practices of men of another generation. We have grown accustomed in our day, at least some of us have grown accustomed,

to speak of our psychotherapeutic efforts and experiments in fairly forthright fashion, not deeming it so necessary as formerly to neurologize our thinking, nor to hematologize, nor to vascularize nor otherwise to try to translate into some other form of medical jargon the human facts with which we deal. When reading any old writer on the medical arts we should, I presume, prepare and utilize for each a sort of conceptual slide-rule which would help us to calculate back into actual behavior the actions and words which he may have used, but which, for publication, he had laboriously elaborated into the special medically acceptable idiom of his time and of his personal predilection.

To be more specific, let us consider Benjamin Rush. He is spoken of as the father of American psychiatry. His portrait is the emblem of the American Psychiatric Association. He developed the first systematic theory of insanity formally propounded in America. He considered insanity to be a disease of the blood vessels, and his enthusiasm for blood-letting as a cure for madness was widely recognized here and abroad. I quote from the 1827 edition of his *Medical Inquiries and Observations upon the Diseases of the Mind*. Rush wrote: (p. 15) "Having rejected the abdominal viscera, the nerves and the mind as the primary seats of madness, I shall now deliver an opinion, which I have long believed and taught in my lectures, and that is, that the cause of madness is seated primarily in the blood-vessels of the brain, and that it depends upon the same kind of morbid and irregular actions that constitutes (sic) other arterial diseases."

Having thus clearly formulated in organic terms his conception of the *proximate* cause of madness, Rush proceeded to a consideration of the *remote* and *exciting* causes. I quote again (pp. 44-45): Madness "is more common from mental than corporeal causes: . . . I have taken pains to ascertain the proportion of mental and corporeal causes which have operated in producing madness in the Pennsylvania Hospital. . . . In 50 (patients), 34 were from mental causes and 16 from corporeal causes . . . but I am sorry to add, my success in this inquiry was less satisfactory than I wished. Its causes were concealed in some cases and forgotten in others. . . . (p. 44) Depression of mind may be produced by (events) that are forgotten; or by the presence of objects which revive the sensation of distress with which it was at one time associated, but without reviving the cause of it in the memory." (This last sentence could be elaborated into an interesting premonition as to the importance

of unconscious mentation.)

Benjamin Rush then gave considerable attention to the methods of therapy which are intended to act through the medium of the mind. Speaking particularly of hypochondriasis, which he called a partial intellectual derangement or partial madness, Rush wrote (p. 104): "The first thing to be done by a physician under this head, is to treat the disease in a serious manner. . . . However erroneous a patient's opinion of his case may be, his disease is a *real* one. It will be necessary, therefore, for a physician to listen with attention to his tedious . . . details of its symptoms and causes." (Here is a shrewd observation of an important psychotherapeutic consideration.)

Rush also advocated employment or business of some kind as a psychotherapeutic measure. He quoted Burton with approval, "Be not idle, be not solitary," but he capped it with a more brilliant suggestion from Johnson, "When you are idle, be not solitary; when you are solitary, be not idle."

Rush has noted, also, (p. 124) the psychotherapeutic device, in dealing with depressed patients, of "mentioning the *name* of a parent, relative or friend" or "carrying the patient's memory or imagination back to the innocent and delightful sports and studies of early life."

These statements by Rush concerning the mental causes and the mental treatment of "madness," are quoted in order to illustrate his knowledge of psychopathological and psychotherapeutic truths, and also to raise the question as to how he reconciled them with his vascular theory of the cause of madness.

I have not found that he offered a fully systematic exposition as to how the mental causes and mental therapies operated upon the *presumed* arterial disease, but a significant indication is given in his discussion of the *indirect causes*, (p. 36): "Madness is excited in the understanding most frequently by impressions that act primarily upon the heart. . . . Some of these . . . are joy, terror, love, fear, grief, distress, shame, . . . inordinate love of praise, domestic tyranny, and the complete gratification of every wish of the heart."

This quotation offers the needed cue, I believe, to the manner of thinking by which Rush was able to combine his psychopathology and psychotherapy of insanity with his vascular theory of etiology. The heart and blood vessels were conceived of by him as the instrumentalities of emotional experience—the physiological mechanism through

which transient influences of an emotional kind produce more enduring effects. His vascular theory of etiology was thus, in one sense, an emotional theory, conceptually somaticized, so to speak, in somewhat the same fashion that Kempf has utilized the autonomic nervous system for the conceptualization of the nature of emotional attitudes.

This brief excursion into the writings of Benjamin Rush is undertaken with the most sympathetic appreciation of his keen observations and shrewd practical sense, yet I wish also to point out, through this illustrious illustration the great defect which I think has limited and hindered Rush, and Weir Mitchell, and others in their attempts to formulate psychotherapeutic principles. This defect is the lack of *psychological depth* in their professional formulations. Ideas about the heart and arteries, or, in Mitchell's case, ideas about fat and blood, have afforded a gratifying basis of rapport with their professional brethren, and served to save them from any threat of professional excommunication, but an unfortunate result was to maintain a level of comprehension too superficial to support the formulation of sound psychotherapeutic *strategy*. Psychotherapeutic tactics were offered in abundance, but not strategy. Consider, for example, this recommendation by Rush for the treatment of a certain specific hypochondriacal complaint (p. 108): "Cures of patients, who suppose themselves to be glass, may easily be performed by pulling a chair, upon which they are about to sit, from under them, and afterwards showing them a large collection of pieces of glass as the fragments of their bodies." Although this manoeuver may perhaps have had some efficacy as a tactical device for defeating a specific hypochondriacal delusion, we would certainly not, in our day, recommend it as a well-considered part of psychiatric strategy in helping such a patient toward sound and enduring health.

The deficiency in psychological depth, and the consequent preoccupation with psychological tactics to the relative neglect of psychological strategy, also tended to vitiate in considerable degree the case-studies on which further progress might depend. Based on a vascular theory of mental derangement the pertinent medical history, as also the course of the disease under treatment, was conceived of as a history of the individual's arterial system. The importance of emotional events was appreciated, but primarily, it would seem, because they affected the heart and thereby the arteries of the brain. Instead of seeking to

understand the biographical development of a personality, as a basis of psychotherapy, what one sought was a catalogue of incidents which might be considered to have affected the arteries.

In the middle of the last century the German psychiatrist Wilhelm Griesinger had a considerable influence in America, as elsewhere, in shaping conceptions of psychiatric therapy.

Now Griesinger is customarily considered to have been the great proponent of the somatological as opposed to the psychological concept of mental disorder. It is true that he was an ardent, and very effective, champion of the idea that insanity is a cerebral disease, and he took great pains in seeking to relate the knowledge of mental disorders current in his day to whatever conditions of the cerebral tissues he could establish or reasonably conjecture; yet he too, as well as Rush, indicated clearly his belief that psychic causes were the most frequent and the most fertile causes of mental disorders. It seems reasonable to assume that many American physicians, reading his textbook may have read through to the back of the book and been influenced in their practical work by his very sensible discussions there of psychotherapeutic measures. I quote several passages from Robertson and Rutherford's translation of the second edition of Griesinger's textbook *Mental Pathology and Therapeutics*, (p. 327):

"Theoretical hypotheses have rendered it difficult for science to recognize the results of experience. . . . It must be remembered that cerebral activity may be modified quite as effectually, directly and immediately by the evocation of frames of mind, emotions, and thoughts, as by diminishing the quantity of blood within the cranium, or by modifying the nutrition of the brain. . . . We have, in the direct provocation of certain states of mind, a very powerful means of successfully modifying disturbances of the somatic state." (p. 328) "Nowhere is it of greater importance than in the treatment of insanity, to keep in view the individual; nowhere is the constant consciousness more necessary that it is not a disease but an individual patient that is the object of our treatment. . . . A penetration into the psychical individuality of the patient is here demanded, which is scarcely ever necessary in ordinary medical practice." . . . (p. 343) "The old ego which in insanity for a long time is not lost, but only superficially repressed, or hidden in a storm of emotion, behind which it remains for a long time capable and ready to re-establish itself, must, as far as possible, be re-

called and strengthened. . . . The moral treatment of insanity is most successful when the *ego*, already formed, fixed, and only temporarily repressed . . . waits the opportunity to resume its former place." (p. 90) "The inquiry into the history of the case ought to embrace the whole of the bodily and mental antecedents of the individual. . . . We must faithfully and intelligently comprehend the relation of the predispositions . . . the education and the governing inclinations of the individual. . . . Only in this way is an insight into the true history of these diseases possible; only thus can we succeed in grasping at their beginnings those fine threads which have ultimately entwined themselves into delirious conceptions; only thus can we . . . recognize the far-back commencement of the preparation for the illness. . . . All of this is of the highest importance in a system of treatment which gathers from the history of the case indications, sometimes for the amelioration of inveterate chronic processes, at other times for the removal of certain psychic causes, and which requires a profound knowledge of the character of the individual to enable us to employ all his inherent resources in support of our active treatment."*

These quotations from Griesinger provide an admirable psychotherapeutic orientation, yet I presume they pictured an ideal, rather than an actual trend in practice. Whoever may have attempted to put this ideal into practice must have been greatly handicapped by the lack of specific guidance. Griesinger presented a much more sophisticated and comprehensive view than did Rush, of what psychiatric therapy might include, but here again the preoccupation with states of the cerebral tissues probably served to hinder the more thorough study, which might otherwise have been carried through—and perhaps brilliantly carried through—regarding the organization and growth of personality and the possible strategic utilization of principles so derived in a more explicit and constructive type of psychiatric therapy.

Throughout the nineteenth century American psychiatry was affected from time to time by reverberations of the European interest in hypnosis as a psychotherapeutic procedure, but, in general, hypnosis fluctuated about the charlatan fringe until near the end of the century, when the Nancy school attracted some American medical men, and Boris Sidis and Morton Prince made extensive use of hypnosis. The

* These statements do not differ essentially from those in the first German (1845) edition, except the quotation from p. 90 which represents a part of the revision for the second edition.

work of Sidis never got into the main stream of psychiatric development, and even Morton Prince felt somewhat outside the main current. When he wished near the end of his life to set up at Harvard the means for continuing researches in medical psychology, it was not done through the medical school or associated hospitals but through the college in Cambridge.

These nineteenth-century trends in psychotherapeutic thought in America to which I have been referring, illustrate, I think, a curious result of the emotional strains aroused among medical men in the consideration of psychotherapy. The Christian Science movement bore indirect witness to this aversion, in taking some principles which had genuine psychotherapeutic significance and expanding them extravagantly into a religious dogmatism, sharply delineated from the medical profession, and even belligerently opposed to medicine. The unpleasant experiences of George M. Beard and of Morton Prince when identifying themselves frankly with psychological modes of treatment were clearer indications of this aversion. But perhaps the more pernicious effects of this medical attitude were exhibited in the work of Benjamin Rush and Weir Mitchell. Steering clear of this aversion, Mitchell cast his psychotherapeutic work into the pattern of a nutritional theory, and Rush put his in terms of arterial disease, both of them failing thereby to establish any psychological depth for their keen psychological perceptions.

The twentieth century began more propitiously for the medical development and use of psychotherapy. In the first decade the invitations to two distinguished Continental visitors, Pierre Janet and Sigmund Freud, bore witness to a considerable desire in this country for psychological insight. Also, in ways indirectly affecting the medical world, the pragmatism of William James and the integrative functionalism preached by John Dewey began to modify academic psychology in directions more readily assimilable to the practical tasks of the physician. Adolf Meyer as a pragmatic clinical scholar, with talents and achievements which commanded medical respect, championed and established a clinical viewpoint, pluralistic yet integrative, in which symbolic intellectual functions and diffuse regulative emotional functions of the organism were simply and regularly required to be taken into the medical account. This view met with somewhat less negativistic resistance than had been felt against presumed "psychological mys-

teries." The one article by Dr. Meyer which has seemed to me to epitomize most aptly his fundamental influence on psychotherapy was the one published in 1915, under the characteristic title "Objective Psychology or Psychobiology with Subordination of the Medically Useless Contrast of Mental and Physical." By the time of its publication, Meyer's influence had already been widely effective in this direction.

I quote one sentence from that paper: "As soon as mental attitudes and mental activities are accepted as definite functions of a living organism, mentation and behavior is treated as a real chapter of the natural history of man and animal, and psychology ceases to be a puzzle supposedly resisting the objective methods of science."

In my studies of Meyer's papers, I cannot see that the development of his very comprehensive views hinged on any one crucial point, but one can see a very important part of his thought in his early conception of the dementia praecox type of reaction as determined in part by bad mental habits, offering therefore the possibility of change.

Meyer did not systematically elaborate specific techniques of psychotherapy. Even the well known Meyerian expression "distributive analysis and synthesis," which was systematically expounded by his pupil, Oskar Diethelm, represented a considerable eclecticism, and Meyer has preferred to consider psychiatric therapy as the application of common-sense to special individuals and situations in the light of all the available facts.

It is no secret that Meyer deplored the denominational features of psychoanalysis; yet, in a paradoxical way, I am inclined to think that the measure of good will which psychoanalysis has gained in the medical profession in this country, and the decidedly medical affiliation and orientation of psychoanalysts here as compared to the Continent, has depended in considerable measure upon the influence of Meyer, and his broad psychobiological orientation in medicine. Certainly the psychotherapeutic trends which Meyer cultivated were strongly opposed to superficial "neurologizing" and strongly encouraged a truly deep and genuine psychological insight.

Since Meyer's breadth of view and depth of understanding brought about in his practice and teaching a medically acceptable meeting ground, the organicist shibboleth has lost much of its divisive force in American discussions of therapy.

William Alanson White also exerted an extraordinarily powerful influence on the psychotherapeutic orientation of American psychiatry. It is of special interest to consider the manner in which he dealt with the organicist medical tradition. In a paper published just 50 years ago, he discussed in a broad way the lesions of the brain which cause cerebral malfunctioning. It is clear in this paper that White's way of thinking at that time required that some lesion be postulated as the cause of any cerebral malfunctioning. He expounded in this paper the concept of two orders of lesions, "molar" and "molecular." Having achieved in theory a molecular dispersion of the rationalistically-required lesion, he subsequently felt free to deal with the personal functioning of the organism, in whatever practical ways might be found, without the compulsion to hypothecate lesions. He had a special talent for administrative leadership and a warm enthusiasm for what could be found practically workable in the Freudian contribution, or in any other promising line of thought; and this combination did much to shape a therapeutically oriented American viewpoint in psychiatry.

The development of psychoanalytic therapy has had a profound influence on all psychotherapeutic work in America. In a direct way, we have had the influence of Dr. Brill, his own work and his translations of Freud's work, and we have had a considerable influx of European analysts and a very extensive training of American analysts. It would be difficult to disentangle which might be characteristically American from the rest of the psychoanalytic developments here. Aside from the technical details of free-association or dream-analysis, and rather independently of psychoanalytic doctrines, psychoanalytic therapy has developed in its practitioners and in those who have been privileged to keep in touch with such work, a solid working-appreciation of personality depth, which has in one way or another, influenced all recent psychiatric thought.

It does not seem profitable at this time to attempt a very detailed consideration of the manner in which specific psychoanalytic discoveries and doctrines have influenced therapeutic trends. It would be very easy to get caught up in minor acrimonious disputes. Yet there is one point concerning psychoanalytic history which affected the general trend of psychiatric therapy in so significant a degree, in my opinion, that I should not feel it proper to pass it by without at least the expression of a personal opinion.

It seems to me that the third decade of the psychoanalytic movement, approximately the time of the first World War, marked a special crisis. What was dynamic and vital in the psychoanalytic appreciation of personality depth had come perilously near to being suffocated in a verbalistic game of erotic symbols and libidinal formulations; but the stirring events of that period and the psychiatric casualties of war brought insistently to attention the need for a broader understanding of *anxiety*, as a fundamental problem in human adjustment, and of *aggression* as a factor in a personal maladjustment. For many psychiatrists also the war brought a more concrete meaning to the concept of the self-defensive nature of neurotic reactions. Not only did the psychoanalysts, as a special group, utilize these considerations for broadening their concepts; other psychiatrists came thereby to a better appreciation of the pathological forces and mechanisms with which they had to cope, in their psychotherapeutic endeavors.

At this point in the discussion it is appropriate to consider a fundamental social principle of modern psychiatric work. I refer to the increased appreciation that neurotic and psychotic reactions, considered as poor or second-rate types of adjustment to life-situations, arise as responses to the tensions of interpersonal attitudes. Somehow, without there being any specific date or situation to which we can allocate the discovery, interpersonal relationships, or rather interpersonal attitudes, have become the very special business of the psychotherapist. Under the intellectual leadership of Harry Stack Sullivan, "Interpersonal relations" have indeed become the subject matter of the special journal which is entitled "Psychiatry." It is a primary aim in the strategy of psychiatric therapy, now, to help the patient to gain emotional security and self-assurance in interpersonal relations. This fundamental trend has many ramifications in current psychiatric practice and research, of which one example requires special mention: the widespread experimentation in group therapy, in which the interactions between the members of a group are utilized for therapeutic purposes.

The rather sudden and remarkable development of child psychiatry in America has been occurring at a time when psychiatrists have been specially preoccupied with concepts of personality structure and personality growth. The increasing appreciation that the childhood years have great strategic importance for subsequent mental health or disorder, stimulated efforts to help children already beginning to exhibit

behavior-problems, and conversely experience with children has served to generate optimistic faith in the potentialities of personality growth, with a bit of help, even under many hindering circumstances. Frederick Allen, in his recent book "Psychotherapy with Children" has given a specially earnest and appealing presentation of a very important modern trend in psychotherapeutic philosophy which rests on a belief in the dignity of human nature and a respect for individual difference. Translated into methodology, such a psychotherapy avoids any dominating attitude, yet avoids inert passivity, and seeks to favor such respectful interaction between physician and patient as encourages the spontaneous and self-assured assumption of a responsible and gratifying social role.

In tracing hurriedly certain main therapeutic trends, I have given primary attention to psychotherapeutic considerations, chiefly because they have served to reflect the general working progress, and incentives, in psychiatry. Even the outspoken organicists whom I have quoted have indicated that in their experience, mental forces seem the main consideration. There is also a further reason. Psychotherapeutic experience and thought have largely shaped the growing concepts of *personality*, which at present dominate psychiatry to the extent that the term "personality disorder" is often now used as a practical synonym for any condition which is thought to need psychiatric attention.

Many of us are customarily disposed, now, to look upon the organic and toxic factors in psychiatric conditions as influences which *limit* or *bind* the person in his adjustive behavior, spoiling his good performance and providing the occasion thereby for poor personal functioning in a manner largely determined by the personality. This formulation represents in my opinion, a more useful and stimulating view, than to look to the organic conditions as the direct causes of specific items of pathological behavior. It is nevertheless considered exceedingly important, for the purposes of psychiatric therapy, to combat these noxious organic or toxic conditions with the best means available, and to seek better methods of doing so; also to enlarge our knowledge of these noxious organic influences. Endocrinological dysfunctions and nutritional deficiencies also receive attention, by a similar rationale, in psychiatric treatment.

The impressive success achieved during our generation in the treatment of syphilitic disease of the brain has been an enormous stimulus

to the therapeutic enthusiasm of psychiatrists. The success of Wagner-Jauregg's malaria treatment of general paresis undoubtedly served to justify and encourage therapeutic trials of very bold measures for other psychiatric conditions, culminating in the shock therapies. The Sakel method, utilizing hypoglycemic coma induced by insulin, for the treatment of schizophrenic conditions, was the starting point about ten years ago for an extraordinary trend in psychiatric therapy, which may be characterized as the employment of a direct and violent attack upon cerebral tissues considered to be functioning in a pernicious way. This trend is still strong. It has brought us prefrontal lobotomy and metrazol, also. The favorite technique in shock therapy now—the use of the faradic electrical current applied to the skull—has greatly changed the current practices in the treatment of depressive states, by putting into the hands of the psychiatrist a means, often successful, for interrupting quickly the guilt-laden ruminations of the patient. The throwing of the electric-switch has not solved all the personality problems of these patients, but this method has added a new and powerful tactical resource, whose possibilities challenge us to learn how to employ it in a sound psychiatric strategy.

SHOULDER PAIN AND DISABILITY*

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AT first glance one would think of this subject as one of rather limited scope. Immediately, however, on investigation of one's clinical experience with pathology and symptomatology in this region of the body, one's respect for the multiplicity of abnormal conditions which may here cause disability or symptomatology increases. Respect is enhanced and interest intrigued by the structural and mechanical difficulties arising in this location tending to prevent improvement of function or relief of symptomatology when abnormal conditions are present. Even should one limit one's self to a consideration of just the shoulder joint and not the shoulder region, a great amount of material would present itself for discussion. This afternoon we shall consider the shoulder in its broader sense. If, therefore, we discuss briefly some phases of pathology and symptomatology and slight others altogether, we hope for your indulgence in order that we may refer to certain lesions in greater detail which we consider more common or more important.

One can group all pathology causing pain or disability in this region under six convenient headings:

1. Distant lesions causing radicular pain
2. Pathology of the muscular structures
3. Lesions of the acromio-clavicular joint
4. Arthritic pathology
5. Pathology in the bony structures
6. Lesions giving symptomatology due to or simulating that of tendon or bursal pathology

1. *Distant lesions causing radicular pain*

Pain located in the shoulder region, and frequently sharply circumscribed to the shoulder joint region, arising from pathology at a distance, is well known to occur. The most common cause of such discom-

* Read January 15, 1943 in The Friday Afternoon Lecture series of The New York Academy of Medicine.

fort is probably radicular pain caused by irritation of nerve roots as a result of pathology in the cervical spine. The formation of arthritic spurs encroaching on the intervertebral foramen or the lessening of the diameter of these foramina by loss of disc substance due either to arthritic change or trauma frequently causes such manifestations. Small subluxations or unreduced dislocations are frequently first noted due to radiation of pain to the shoulder. Cervical rib or the scalene syndrome, while classically distributing pain and other symptomatology farther along the upper extremity, frequently early in their course cause radiation of pain to the shoulder. Syringomyelia in the cervical region may produce as one of its major symptoms a Charcot destruction of the shoulder joint. The above facts are so well known to this audience that no apology need be made for stating that cervical x-rays are necessarily a part of any satisfactory examination of the shoulder region where difficulty arises in diagnosis. Not only does interference with the direct nerve pathways to the shoulder cause pain here, but it is interesting to remember that pathology as far away as the gall bladder on the right or cardiac lesions on the left may be responsible for symptomatology in this location.

Fortunately, difficulty in ruling out true shoulder pathology in all the above lesions is slight. This is the only one of our group in which, on careful examination, no pathology is found in the shoulder itself. There is no loss of motion, spasm, protection, localized tenderness, deformity, paralysis, displacement of bony structure, change from the normal contour, or pathological x-ray findings. This does not mean that location of the pathology causing referred pain is in itself not difficult. It well may be. Absence of the above findings, however, immediately limits one's search and refers one's attention elsewhere.

2. *Pathology of the muscular structures*

Because of the complexity of the muscular arrangement and the fact that stability of this joint is mainly provided for by muscles, simple myositis as a result of overuse is frequently encountered. In addition to this, lesions causing general muscle irritation, such as trichinosis, may present continuing symptomatology here long after it has disappeared elsewhere in the body. We have encountered two cases of trichinosis simulating disability such as would ensue from injury to the capsule or the short rotator tendons of the shoulder. A relatively rare but extremely interesting condition, myositis ossificans, frequently begins in this location.

Paralytic lesions in this region are likewise of more prolonged duration and more difficult in treatment because of the mechanical disadvantages present. Poliomyelitic manifestations especially of the deltoid demand prolonged support in an awkward position which is frequently difficult to enforce. Paralysis of the serratus magnus muscle causing winged scapula not only demands prolonged support but such support is difficult to obtain. Axillary nerve damage is an extremely difficult lesion to treat. This nerve is almost impossible to repair if torn and the lesion is frequently overlooked for a considerable period of time.

Fortunately, in spite of the difficulties presented, much may be done for improvement and alleviation of dysfunction even in the more serious type of muscular lesion. This is well shown in cases of Erb's palsy where release of tight muscular structures may massively overcome the deformity present as well as in paralysis where transplantation of muscles may restore at least partial function.

3. *Lesions of the acromio-clavicular joint*

Lesions of this joint, being structurally near the shoulder joint itself, frequently are confused as being the cause of symptomatology in the shoulder. Careful and critical examination will quickly establish the true location of pathology. In spite of this we frequently see mis-diagnosis due to dislocations of the acromio-clavicular joint. Probably even more frequently we find infectious arthritis of the acromio-clavicular joint (especially tuberculous arthritis) mis-diagnosed as shoulder pathology.

4. *Arthritic pathology*

Probably more cases of shoulder dysfunction belong truly under this classification than among all the other groups combined. To belong rightly under this classification, however, a case should arrive there by exclusion. Rheumatism of the shoulder is altogether too easy a diagnosis. Various forms of arthritis are seen. Their features should be noted and clear-cut classification made. Improvement in treatment and benefit to the patient can thereby be greatly enhanced. Hypertrophic excrescences mechanically blocking motion can be removed successfully. Associated bursal and tendinous adhesions can be broken under general anesthesia by gentle manipulation or divided by sharp dissection when necessary. Great care must be taken to rule out a tuberculous etiology, and even with great care occasionally such cases will progress for a long period of time before their true nature is recognized. One should always suspect

the so-called infectious type of arthritis which persists for a long period with steady progression despite satisfactory treatment. An acid-fast basis may be present. It is not necessary herein to review the treatment of arthritis. We would urge to your attention, however, that arthrodesis of the tubercular shoulder is imperative. One might also well consider the availability of arthrodesis for the shoulder destroyed by any arthritic process. Relief to patient and restoration of at least partial function of the extremity may thereby be given.

5. *Pathology in the bony structures*

There are many lesions of the upper humerus and of the scapula which cause dysfunction of the shoulder and pain in this locality. The most frequent are tumors, infections, fractures, dislocations, and subluxations.

The same tumors both benign and malignant may be present in this locality as are found anywhere in the osseous system. Osteochondromas of the scapula may cause disability by their size or their impingement in motion on other structures. They may similarly be located on the upper humerus and may be called to the patient's attention either by the presence of their mass or by pain. Fibrocystic lesions in the upper humerus are very frequent and though they may cause a low grade pain, they are frequently first brought to the patient's attention by pathological fracture. Giant cell tumors are likewise frequent in this same location, are closely allied with fibrocystic bone lesions and their symptomatology and treatment are similar. Central chondromata produce low grade expansible-type pain whose cause can be determined only by x-ray.

The malignancies are represented in children by sarcoma and in the adult by metastatic carcinoma. Though sarcoma is generally accompanied by low grade pain, carcinoma may manifest itself only by pathological fracture.

Of the infectious lesions at the shoulder, osteomyelitis of the upper humeral metaphysis is much more common than suppurative arthritis of the joint.

Fractures of the surgical neck of the humerus frequently occur especially in older people without displacement and unaccompanied by the severity of symptomatology frequently seen in fractures elsewhere. They are often treated as sprains. X-ray where shoulder symptomatology exists will establish the condition present. Frequently, where such

fractures have been more severe, anatomical reconstruction is impossible and a certain loss of function of the joint is inevitable and must be accepted. Fractures of the scapular glenoid are often present and unrecognized and account for chronic shoulder subluxation and disability. Fractures of the base of the coracoid process are occasionally associated with acromio-clavicular dislocation making difficult its replacement and retention. This may promote shoulder dysfunction through lack of support.

Recurrent dislocation of the humeral head from the glenoid is often accepted by the patient and his physician as a minor disability. We feel strongly that all such recurring dislocating shoulders should be surgically repaired.

6. *Lesions due to or simulating that of tendon or bursal pathology*

All such lesions can be conveniently grouped among those due to:

A. Pathology in the tendons

B. Pathology in the bursae

C. Pathology in the adjacent bony structures

There are four flat tendons above the head of the humerus reinforcing and becoming part of the capsule. From the front to the back these are the subscapularis, the supraspinatus, the infraspinatus and the teres minor. Partial or complete laceration of one or all of these tendons may occur giving great disability. Such laceration practically always occurs when the arm is forcibly abducted as in falling on the outstretched hand. We have never seen laceration present when the patient gave a history of falling and striking on the point of the shoulder. Disability ensuing depends upon the amount of laceration present. Such laceration, except in the case of the subscapularis and possibly the teres minor tendon, do not tend to heal. This is undoubtedly because of the inability to secure good blood supply in tendons jammed between the head of the humerus and the under surface of the acromium process as well as because of the distance of separation at point of laceration.

Symptomatology will depend upon the amount of laceration present. With slight laceration of one tendon, motion of the shoulder may be complete but there will be localized tenderness at point of laceration, loss of strength in abduction and pain in lowering the arm as the greater tuberosity of the humerus passes out from under the border of the acromium process. As the amount of laceration increases, symptomatology and loss of strength will increase until finally, if two or

more tendons are lacerated, active abduction cannot be carried out beyond the point at which the greater tuberosity of the humerus impinges against the outer border of the acromium process. Passively the arm may be carried through full range of motion. If of long standing, adhesions may have developed limiting passive range of motion. Diagnosis in great part may have to rest upon history of mode of injury and suspicion on the part of the physician that such basic pathology may exist. Since laceration may be minor, or indeed, traumatism may have occurred without actual laceration, a short period of observation and physiotherapy is permissible. If symptomatology should persist beyond one or two weeks, exploration and repair are indicated. Otherwise great and permanent disability to the shoulder may result. Late repairs are extremely difficult and are unsatisfactory. Where complete laceration of the whole cuff of four tendons has taken place, or where the laceration has existed many months and a badly disabled upper extremity has resulted due to shoulder instability, shoulder fusion may restore a good degree of usefulness to the extremity. Resulting motion will be carried out by rotation of the scapula upon the thorax.

Early repair of incomplete lacerations of this muscular cuff are uniformly very satisfactory. Postoperative treatment, however, is long and a great amount of physiotherapy is necessary before satisfactory result is secured. Instances of laceration of these tendons by rough manipulation in reduction of dislocation of the shoulder or by attempts at reduction without the relaxation of good anesthesia have been encountered. May we therefore warn you in reducing dislocations of the shoulder always to use gentleness, steady traction instead of manipulation, and satisfactory anesthesia to secure perfect relaxation wherever necessary. When complete avulsion of all four tendons has occurred the cuff torn off will frequently turn downwards over the glenoid and the humeral head will lie on top of it. Hence, the shoulder will give an appearance of unusual instability with recurrent dislocation. Therefore, in cases where dislocations recur almost as rapidly as reduction is secured, this lesion should be suspected and surgical inspection and repair made. Laceration of the long head of the biceps frequently accompanies major cuff tears. It should be looked for and repaired or transplanted. Where such a condition exists, or indeed where any major laceration of these tendinous structures is present, conservative treatment can be of no advantage.

The greater the amount of laceration, the less will be the spasm, protection and pain associated with the lesion. This is so since the tendon edges lacerated will have withdrawn from any point of pressure between the humeral head and the under surface of the acromium process in complete laceration. In partial laceration, the defect in the tendinous surface will be impinged upon by the humeral head. This will cause pain, protection and loss of motion. Not only is surgical arthrodesis indicated in cases where complete avulsion of the whole cuff has occurred but also in cases where laceration of the axillary nerve is associated with damage to the tendinous cuff.

Bursal adhesions are frequently associated with small laceration but never with complete laceration of these tendons. When present they complicate the symptomatology and diagnosis.

Definite preoperative diagnosis cannot be made, a diagnosis of internal derangement being preferable. One can be reasonably certain that pathology of the tendinous structures is present but its definite extent and nature cannot be foretold. As most lacerations begin on the deep surface of the tendon and frequently do not extend completely through its thickness, a normal tendon surface may be seen on exploration when first entering the bursa. Through a small incision anterior to the supraspinatus the under surface of the tendons can be explored with a small curved clamp for laceration and repair carried out if found. In this same manner horizontal splits within the tendon substance will likewise not be overlooked.

Calcification of the subdeltoid bursa is probably always an end result of calcification of the supraspinatus or other tendons of the rotator cuff. Such calcification probably occurs in an area of degeneration resulting from previous horizontal split or localized trauma to the tendon. Needling these lesions or washing out the calcium with through and through irrigation generally gives relief. Certain of these lesions cannot be successfully washed out. On exploration such lesions have been found to be not only calcified but actually ossified. Their surgical removal has given satisfactory relief. It is likewise to be noted that recurrence of calcified lesions frequently takes place. In such instances surgical exploration, with curettage of the degenerated area has given lasting relief. If calcification of the tendinous area does not cause symptomatology enough to demand attention it frequently finally ruptures into the subdeltoid bursa. Thereupon immediate intense pain, loss of

motion and disability ensue. Washing the calcium out of such bursal lesions is very much easier than it is from the small tendinous foci, but of course, leaves the original focus behind.

Other lesions of the subacromial bursa beside calcification occur. Laceration of the floor without laceration of the underlying tendon has been seen. Symptomatology here resembles that of mild laceration of the tendinous cuff but recovery is much more rapid. Frozen shoulder or adhesive obliterative bursitis may vary in the extent of the process and the amount of symptomatology. Partial limitation of motion of the shoulder joint with extreme pain at limits of motion represents incomplete obliterative adhesions. Most of these adhesions are located about the subscapularis tendon as noted on surgical inspection. The typical cases in which the patient holds the arm rigidly to the side and refuses any attempt at motion of the shoulder joint (with extreme pain causing loss of sleep and unrelieved by physiotherapy over considerable periods of time) represent almost complete involvement of the bursa. Frequently, adhesions in both these types of cases can be broken under general anesthesia by manipulation with moderate force. Occasionally, even with extreme force, adhesions in this latter type of case cannot be so broken. In such instances we have surgically divided through the plane of the original bursa, having found it to be represented by a fibrous raphe. In these instances prolonged support of the extremity in abduction and subsequent physiotherapy for many months have given excellent results. Occasionally, continuous physiotherapy of heat, massage and gentle stretching without forcible manipulation under anesthesia will secure recovery.

Certain lesions of the bony structures have been found to give symptomatology similar to that of laceration of the tendinous structures or bursal lesions. Avulsion of the greater tuberosity of the humerus in fracture dislocation of the shoulder represents laceration of the prolongation of the tendinous cuff through the bony substance. Such fragments avulsed should be accurately replaced surgically to secure the best eventual function. More complete and more rapid recovery will follow such procedure. Occasionally, avulsion of the superior border of the greater tuberosity may be present. Similar surgical replacement is indicated. Sharp exostoses beneath the bursal floor and arising from the upper border of the greater tuberosity of the humerus may give symptomatology similar to laceration of the supraspinatus tendon. Sur-

gical removal of such exostoses by turning back the bursal floor and later replacing it has been found to give satisfactory results.

A type of case has been encountered giving the exact symptomatology of supraspinatus or cuff damage. It is due to early osteochondritic change within the humeral head. We have found this impossible to diagnose accurately preoperatively. Therefore, if at time of operation no pathology is found in the tendinous cuff, the underlying cartilage over the humeral head should be well explored for cartilaginous changes, especially near the attachment of the rotator cuff. If such osteochondritic change is massive, no surgical relief is possible aside from shoulder arthrodesis. Where small areas are involved the cartilaginous defect can be removed and satisfactory shoulder function preserved.

The diagnosis of lesions causing disability and pain about the shoulder joint depend on careful attention to history of onset or causal factor, precise localization and estimation of objective and subjective symptomatology, combined with accurate mental visualization of the anatomy of the region. Comparatively recent developments in treatment provide a much better outlook for relief of pain and reestablishment of function in this joint.

MORELAND COMMISSION INVESTIGATION

The New York Academy of Medicine wishes to record its position at this time with specific reference to the findings of the State inquiry held by the Moreland Act Commissioner in 1943 on the administration of the Workmen's Compensation Law.

Evidence has been presented indicating that rebates from a commercial laboratory, averaging about 40 per cent of the sums paid by carrier companies have been given to some physicians referring diagnostic work to the laboratory.

It has been further indicated that physicians have loaned money to an auditor of the State Insurance Fund, possibly to ingratiate themselves and to insure approval of their charges made for professional services to claimants in compensation cases.

The intent and effect of both actions have been detrimental to professional ethics and costly to the carriers paying for such medical services. Both are in complete disaccord with the physician's admitted obligation to protect his patients personally and economically. Both involve the division of fees—condemned under the Academy's Constitution and in direct violation of a member's pledge.

The medical profession has been criticized for lack of initiative in taking preventive or punitive action in this matter. Preventive measures can depend for effectiveness only upon the creation of public sentiment for the observance of ethical regulations. This, the Academy, acting with the profession in general, has always sought to do. Punitive action can be undertaken only when valid proof of guilt can be obtained.

In order that the exact facts may be known to the Academy, its Committee on Professional Standards has held a series of hearings with those Fellows whose names have appeared in the press in connection with the matter. In the Committee's report to the Council of the Academy it was stated that while there was a basis for suspicion of guilt in some, though by no means all, of the cases examined, legally competent proof

of guilt was not available to the Committee. Nevertheless, the inclusion of these names in the list of those under suspicion obligates the Academy again to emphasize the responsibility which rests upon every one of its Fellows to avoid any appearance of participation in practices which may reflect unfavorably upon the standing of themselves, the Academy, or the profession at large.

The practices referred to are in the opinion of the Academy entirely contrary to the Hippocratic Oath taken by every physician on the receipt of his medical degree; without his signed pledge to avoid such practices no candidate for Fellowship can be considered by the Academy; and on proof of guilt in such matters, a member is subject to suspension or expulsion from Fellowship.

To those Academy Fellows accused but considered innocent the following letter was sent:

Dear Doctor:

The Council of the Academy has reviewed the evidence presented to it by the Committee on Professional Standards concerning the matter of rebates recently purported to have been given or received by certain Fellows of the Academy. The Council and Committee are convinced of your innocence.

Although it is apparent that responsibility for your association with this most unfortunate publicity cannot be said to rest upon any deliberately unethical action on your part, the Council must again emphasize that Fellows of the Academy must avoid any appearance of participation in practices which may reflect unfavorably upon the standing of the Academy and the profession. It is convinced that the avoidance of suspicion of unethical practice will always necessitate the refusal to accept anything which might be construed as representing a gratuity or a commission.

Very truly yours,

To those accused and failing to establish their innocence and to those considered guilty, the following letter was sent:

Dear Doctor:

The Committee on Professional Standards has reported to the Council of the Academy in regard to its hearing on your case in relation to the findings of the Moreland Act Commissioner on the administration of the Workmen's Compensation Act.

The Council has reviewed this report. It does not intend to take or recommend action for expulsion or suspension until such time as the evidence that may be available to the State has been legally presented. It has determined, however, that in the light of the report of the Committee and the findings of the Moreland Act Commissioner,

it should request your immediate resignation as a Fellow of the Academy.

Very truly yours,

The following addition has been made to the pledge signed by applicants for Fellowship in the Academy:

The undersigned hereby agrees to accept the Council of the Academy as the sole and only judge of his qualifications to remain a Fellow.

Article IX, Section 1, of the Constitution of the Academy is in process of being amended to define more fully the term "fee-splitting" and "rebating."

HERBERT B. WILCOX, *Director*.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



SEPTEMBER 1944

RECENT ADVANCES IN KNOWLEDGE
RELATING TO THE FORMATION,
RECOGNITION AND TREATMENT OF
KIDNEY CALCULI*

ALEXANDER RANDALL

Professor of Urology, University of Pennsylvania

I APPRECIATED tremendously your invitation to be present today, as well as your suggestion that the title of my remarks be, "Recent Advances in Knowledge Relating to the Formation, Recognition and Treatment of Kidney Calculi." It makes me think that perhaps I have had some influence in the elucidation of the etiology of renal stone. Unfortunately, the past few years have not allowed of further efforts in the research, and I am afraid we will have to spend a little time in reviewing the subject as studied by others, and balance their views against the theories and ideas propounded by me some years ago. As Hugh Cabot said before a group of urologists, "while cancer is our greatest problem, it belongs to all medicine, but kidney calculus is essentially a urological problem, and it belongs especially to urologists to solve."

Perhaps you will be interested in the way our work got started. Back in 1926 the American Association of Genito-Urinary Surgeons

* Presented February 25, 1944 in the Friday Afternoon Lecture series of The New York Academy of Medicine.

was meeting at Hot Springs, Va., and not being a golfer, I cornered your E. L. Keyes with some relevant questions and ideas, and it was his interested response that started the ball rolling. As the answers were not clear-cut, he suggested that we get pencil and paper and draw up specifications of what we knew and what we would like to know. Several other non-golfers joined us, and on the veranda of the hotel we gathered around a table and put down what was actually known. In so doing we found many things that were only roughly surmised, and these we proceeded to tear limb from limb. We ended with a clear estimation of what was trustworthy and what we actually did have to know and have to prove. Take, for instance, this statement by Howard A. Kelly, which is all that he could put down as fact in 1922 in regard to the etiology of renal stone formation: "The essential conditions which lead to stone formation in the kidney are imperfectly understood. Race, age, sex, habits, diet; none of them seems to play a great part." He then reports 30 cases, giving their stone characteristics, and describes each; the analysis of single, of multiple, of unilateral, of bilateral, of right-sided and of left-sided stones, and was "astonished to observe how closely his results agreed with those of other observers." Pages are devoted to age, to sex, to race, and to geographical locality, again with surprise at how closely his figures compare with others' reports, and he concludes with this statement under a heading, "Determining Factors": "The questions as to what determines the formation of stones in the kidney cannot be answered at the present time." (1922) Hinman (1935) says: "No more is known of what starts the mechanism of formation of stone than of the mechanism itself." A. J. Scholl (1936) says: "The etiology of urolithiasis is far from clear." And Hugh Young (1926): "The formation of stones in the urinary tract has long been a problem of the greatest interest and difficulty, both to pathologists and urologists. . . . while modern diagnostic methods have greatly improved the treatment. . . . yet the inability from which we still suffer, surely to prevent recurrences, makes the therapy of the disease unsatisfactory." And Keyes, in his *Urology* of 1917, frankly states, "The causes of stone formation are extremely obscure."

So in 1926, at the Hot Springs, we all placed our cards on the table face up, and the distressing ignorance was certainly stimulating. The question was asked, how does a stone start?; and all agreed: as a tiny crystal or a tiny cluster of crystals. But why is it not immediately

washed out of the pelvis? Perhaps some are; but some are not. Why? Where do they lodge, and why there? This constituted *problem number one*. The pelvic wall, simple and not undergoing any frequent pathologic change, was quickly ruled out; but keeping under suspicion the renal papilla. The *second problem* was the realization that stone may be composed of at least eight different salts, and the fact that they occur in urine that at one time is characteristically alkaline, and at another time highly acid, with all steps between. These facts do not help, except to exclude two often considered etiological factors, infection and stasis. *Problem number three* was the time factor, how long does a calculus take to grow to recognizable size? It is certain that a lot of them are found incidentally, and not until they start to pass, and cause ureteral blockage, do *clinically recognizable* symptoms develop. I watched one such over a period of four and one-half years, before an aeroplane trip caused dislodgement, followed by ureteral and kidney colic and, in seventy-two hours, the stone's expulsion! Diet is a frequent cause among theorists, but it falls far short of answering any of our problems, except perhaps that it plays a part in the stone's composition and which salt may predominate: this became *problem number four*. Why stone in one side at a time? There is no predominance, and while bilateral calculi are not unknown, bilaterality is rare in the majority of early cases. What causes the selection of one side, while the other remains in health, became *problem number five*.

And so we discussed and wrote down our ignorance. No one of the five, or more, problems seemed insurmountable; yet our knowledge seemed to have taken off on any one of the various tangents, and investigators seemed in each case to have spent great effort to prove a pet theory in the face of self-evident facts to the contrary. It was illuminating to see how such a group could pool the resources of medical knowledge, and how easy it was to write the specifications of what we really wanted a research to bring out and to prove.

I got off to a poor start with the idea that we wanted to create lesions and then sit back and watch stones grow, but when insurmountable difficulties arose, and stones did not grow, I awoke to perhaps the most salient fact, that it was not given to us to imitate nature and make it fit into our preconceived ideas. It was then that we chose simply to study nature and to study what occurred, and I was glad to have recourse to a large amount of autopsy material. To be sure, we

changed some of our previously held ideas, such as the prescribed methods of examining kidneys, and we opened the pelvis first, searching for pathologic states. It bore fruit. We entered the field convinced by reasoning that we should find precalculus lesions and, secondly, that we should look and expect to find such a lesion on the renal papilla. That is a true precalculus lesion. Perhaps this is the one true fact that we have uncovered, and it is my sincere regret that stress of work and present shortages of personnel have temporarily stopped our further search as to cause and perhaps prevention.

Etiology: Now it has been said, when evidence appears to be confusing, that it is wise to make simple decisions, and that wise decisions must harmonize with the fundamental truths of human nature. Certain it is that the work on the etiology of stone has produced a very confused atmosphere; some of which bears little scientific fact, while some is entirely too ultra-scientific to be of clinical value. As we approach the problem, let us first make some simple decisions. First, let us restrict ourselves to the problem of renal calculus only, omitting all reference to ureteral and vesical calculus; second, let us restrict ourselves to a study of the early, the small, the simple, uncomplicated renal calculus. This I believe a wise decision, in order to avoid the confusing evidence and the conflicting ideas when more than one pathologic state is existent. This brings us directly to the study of what is known as the "primary renal calculus," and sets aside the "secondary calculi" where other possible conditions may have etiologic bearings.

Now may I make a few statements which I believe are axiomatic statements that are again wise decisions and do not bear refutation. The first negates what I have just said, for except as it is made to apply to the clinical picture alone, there is no such thing as a primary renal calculus, there is no such thing as "calculus disease," all books to the contrary, except as a clinical entity, there is no such clinical entity until a calculus attempts to pass and causes urinary stasis and renal colic, and I would be so bold as to say that near to 10 per cent, nay, even 15 per cent, of those here present in this room have today, now, the precursors that may later cause stone to develop in a kidney. I put it this way for I am most anxious to bring to your attention a second axiomatic statement, that renal calculus is, in the final analysis, and has to be, only a symptom; a symptom that takes its origin from some precursory pathology, and it is this precursory pathology to

which we must direct our attention when we wish to seek the real etiological reason in any given case.

Two additional axiomatic statements must be made to clear our picture further: The first is that these complicated crystalline calculi, while greatly differing in their chemical structure, the one from the next, are nevertheless composed under a single chemico-physical law governing all crystallization and are, without exception, composed of salts common to the urine of all mankind, with the rare and few exceptions, cystine and xanthin, in which cases they are recognized as the common and expected urinary products in those especial patients. The second statement worthy of comment and accentuation is the time-consuming interval during which growth of a calculus is gained. An interval frequently of months and of years is required for the slow crystallization and growth of a calculus, but most important of all is the recognition that this interval is one devoid of those clinical symptoms which we are most likely to attribute to the existence of a renal calculus. We must disassociate in our long-trained minds the clinical picture that springs into existence when those two words, renal calculus, are used, and then bring forward the pathologist's impersonal viewpoint when we start to search into the early stages of calculogenesis, for these early stages are themselves as impersonal and as non-clinical as the origin, the growth and the existence of a phlebolith.

And finally, I wish to make the most positive axiomatic statement of all, one on which I feel the most emphatic, and one to which we must turn and must understand, if the science of reason and logic is to prevail, and the problem of the etiology of primary renal calculus is to be solved. This statement is that there has to be a precalculus renal lesion, an initiating lesion, a true pathologic condition existing in the kidney pelvis before the first microscopic crystal of a future calculus is laid down upon it as the necessary and essential nidus. Please grasp firmly upon the statement, a calculus has to be but the symptom of a pre-existent pathologic lesion!

So with these basic, truly axiomatic facts at hand, let us look at our problem and analyze what we can from our knowledge of today. Let us forget, for the moment, the picture in our clinically trained minds and our roentgenologically trained eyes and go back-stage, away from the actor who has been strutting these centuries before the footlights, and try to see and reason out what "makes the thing work."

That then will be the etiology.

I do not want to confuse the picture. I truly want to simplify it, even if I open myself, in the discussion, to heinous errors.

Let us look at the thoughtful and very acceptable theories that have been presented and well defended as the possible cause of renal calculus, and let us try to fit them into our need for a pre-calculus lesion and nidus:

Hyperexcretion: Probably the largest single factor that can be held responsible is the condition in which the kidney is putting out a urine overloaded with a single excretory salt. The simplest example is the hereditary cystinuric; right after him comes the patient suffering from hyperparathyroidism and eliminating hypercalcinuria; and third comes the experimental animal overfed with oxamid and excreting a hyperoxaluria. There is no essential difference between these three. The cystinuric is our perfect experimental animal, and from him we should get valuable evidence. In order to prove one of our axiomatic statements, let me ask, why do only 2.7 per cent (Hinman says 3 to 5 per cent) of the recognized cystinurics develop stone, and why does he first form a stone in only one kidney and in only one calyx of that kidney? Do we need more to make us think that there must be a reason at that point, that there must be a precalculus lesion, yes, a *precalculus* lesion? The initiating lesion! And from this I believe we are on perfectly safe ground to reason by analogy into and through the hyperparathyroid and oxamid groups, noting in passing that each group entails the same etiological and pathological sequences, but each working with a different salt. The first forms a cystine stone, the second forms a calcium phosphate stone, and the third forms an oxalate stone.

Do bear with me. There are a lot of complicating factors and unexplained observations. Let me give you an example. We had a lad of eleven years, an hereditary cystinuric, with a large single stone in his right kidney which was surgically removed and a nephrostomy drainage placed. Apparently it was a perfect differentiating state, for his nephrostomy drainage equalled his left kidney's voided urine. Dr. Andrews of the Department of Physiological Chemistry was interested, and for twelve days we continued the separate collection of each kidney's daily excretion, running as high as 480, 940 and 1050 cc. from the operated side alone. Imagine our surprise when it was observed that the unoperated left kidney continued to put out a cystinuric urine, and the oper-

ated right kidney drainage (this the kidney which had made a cystine stone) was totally free of any cystine! That the observation was perfectly balanced and repeatedly proven I need hardly say (see *J. Urol.*, 37: May, 1937, p. 655). Other excretory products were equally eliminated, but cystine was totally absent from the operated side. The fistula was allowed to heal and the boy was kept under repeated observations, and seven months later a cystoscopic differential catheterization proved that both kidneys were excreting a urine containing an equal and equivalent amount of cystine. We cannot yet explain this anomalous and confusing observation.

But these vagrancies must not be allowed to disturb our study of simple facts, for there has to be a large group of related and, at times, significant factors in our completed study. They are like the artist's gifted brush strokes that paint the background to the portrait, real, necessary, positive strokes, but we must not let them carry our attention away from the essential subject. Such is but one of the vagrancies that has helped to confuse the study in the past, and must be set aside, for the moment, in our effort to simplify the problem and cover the majority of ordinary cases.

Let us pass from the aforementioned studies, the simple, physiologic and hereditary cystinuric, the pathologic and acquired hyperparathyroidism, and the experimental, overdosed oxaluric animal; pass on to another theoretical cause and gaze on it with the same background as the foregoing; i.e., the theory of the role of hypovitaminosis A, which today includes the entire role of dietary causes. Such hypovitaminosis is accompanied by two (really three) urinary changes: (1) a consistent alkaline urine reaction, (2) a disturbance in the normal calcium-phosphorus ratio and a distinct phosphaturia, and (3), if you will, early urinary tract infection. I would like to limit this phase of our subject to the simple chemical disturbance in the urine and place these cases in the group of hyperexcretion, as seen in the cystinuric, the hyperparathyroid and the oxamid-fed animal; but other factors enter, and I wish to use them in the role in which they appear as vagrancies to the composite whole, and as factors in stone's occurrence and growth. I refer to the degenerative changes in the epithelium of the urinary tract under vitamin A deficiency, changes even to desquamation, and to the early spontaneous infection of the highly alkaline urine. Both of these coincidental factors can be recognized as contributory to crystalliza-

tion and, hence, to calculus formation. In fact, Higgins (1935) reported the interesting observation that acidification of the urine by drugs decreased the incidence of stone in animals on vitamin A deficient diets. I believe that the work on hypovitaminosis, and it is practically all animal experimentation, and devoid of human clinical studies or proof, is but another phase of an hyperexcretory state, plus local urinary tract damage, wherein such damage enters to act as the nidus about which the disturbed urine is given a chance to crystallize and form stone.

And now we are left with two further problems to elucidate and to correlate with both fact and theory in the etiology of calculus. The first is the individual who forms pure uric acid (or urate) stone, and the same in regard to the growth of pure oxalate stone; while the second problem is the role of infection.

It is difficult to make the uric acid-urate problem as plain and as simple as the previous cystine story, unless one be allowed to reason by analogy. It appears to be a complete reversal of the hyperparathyroid and the hypovitaminosis problems, as an extremely acid urine is characteristic of these uratic cases, and it is my belief that again a metabolic disturbance, probably in protein metabolism, and perhaps of liver origin, is fundamentally at fault. Certain it is that these patients who continue to pass uric acid stones (I have one who has passed 33 calculi, and another 58) constantly void a urine with a pH of 5.2 or lower, and while they frequently have attacks on first one side and then the other, I have been completely unable to demonstrate, on exhaustive studies in several such, any one thing that suggested correction; and they live happily and they form no more stones as long as the urinary pH is kept between 6.0 and 7.0.

The oxaluric also lacks all explanation as to why he so crystallizes his calculus. What we know is that it is rather characteristically single, is rarely a repeater, is extremely slow-growing and in the kidney is usually small. We know nothing that is associated with the state that bears any possible etiological significance, except that oxaluria is not a rare clinical observation, and the probable relationship to ingestive, digestive and eliminative irregularities, plus the high concentration of oxalates in certain foods.

It is my firm conviction, from the foregoing facts, that an hyperexcretory state, either periodic or constant, rules the chemical type of stone that will form, but truly plays no causative part in deciding where

or when a calculus will appear.

I have attempted to clear the picture of etiology as it may be related to four of the theories advanced, and now we come to the last; i.e., the role of infection. I do not wish to attempt an analysis of the voluminous literature that has developed, but only to point to the failure of this theory to meet the requirements necessary to a factual answer. First, let me refer to the microscopic observations on human kidneys studied in our autopsy series. In 65 of them actual calculi were present, and in 227 cases papillary calcification was observed; but in only 17 out of these 292 could we demonstrate, on microscopic study, actual evidences of infectious reactions to be associated therewith. I mean the observation of organisms, of round cell exudate and of necrosis, the picture of infectious activity as ordinarily understood and observed was absent. Second is the wide variety of organisms as observed by reporters, we having recorded 15 different organisms in 39 clinical cases. And third is the high percentage of reported sterile cases in series which the reporter himself was anxious to prove infectious, a percentage of even one-third of the cases studied. We have regularly cultured the pelvic urine at operation, not depending on catheter culture, and feeling sure, especially in obstructed cases, that with such a foreign body present the occurrence of an active infection would surely heighten and augment any bacterial process above it. We have reported an analysis of seventy-five such cases, selecting only the simple ones and omitting the evident, drastic cases of calculous pyonephrosis of long standing. In thirty-six instances, or 48 per cent, such cultures of pelvic urine were sterile, though urinary obstruction from ureteral blockage by stone was present in practically every one. A very recent case records the point at issue: a twelve-year-old child with a single stone in each side. Our studies showed a pea-sized calculus almost completely blocking the left ureter, with a rapidly developing hydronephrosis behind it; while on the right was a pelvic calculus, four times as large, but without gross obstruction. One might ask which side would be most likely to be infected? There had been no cystoscopy and no ureteral catheterization. I removed the left ureteral calculus, and released a gush of clear urine whose culture was sterile. I then removed the right renal calculus at the same operation, and found a heavy, purulent urine whose culture showed non-hemolytic *Staphylococcus albus*. If our theorizing in regard to the role of infection as a cause of calculus has been willfully dis-

torted by us, don't let us try to distort the truth of facts; for here, in the same patient, at the same time, one side is infected and the other, sterile, with the sterile side suffering the greater insult and damage.

To me these negative evidences speak much louder than the mere finding of an infection in the presence of a stone, especially when we know that such a stone has been relatively long resident in the kidney, and has only recently played an active part in a drastic obstructive uropathy. Perhaps I can stimulate further investigation by being disagreeable and simply saying that local infection does not, or only very rarely can, play any part in primary stone formation, and then hope that some one will promptly jump into the problem and succeed in proving, even to me, how local infection can and does cause primary calculus formation. Watch, please! I'm choosing my words, and do not want to infer "never," for again in creep those vagrancies which all medicine is trained to expect and to accept, but I am sure of my ground in the greater majority. And before dismissing the subject of infection, I want to tell you, again very bluntly, that I believe the products of infection, the toxins of distant infection, of chronic focal infection, of chronic infectious processes, and perhaps of other degenerative processes, do play a very active part in creating renal damage and papillary pathology, which assumes its position as the most important missing link in the origin and growth of a crystalline calculus.

I will show this pathology to you in lantern slides shortly, where I am sure you will be impressed by the clear-cut evidence and be better able to appreciate this simplification of an erstwhile complex problem. I hope you will perhaps even agree with me that, after all, only two essential conditions are necessary, but each necessary, in order that a renal stone may originate: first, a primary tissue damage, and second, a permanent, or transient and oft repeated, hyperexcretory state.

Treatment: There is little I can add to the subject of treatment, except to express my own handling of these cases. It has been a pleasure to have lived through the period when nephrolithotomy gradually gave way to pyelolithotomy. The elder surgeons used, almost routinely, to plunge through the renal cortex for a bloody extraction of a calculus, and left further damage with gross mattress suturing to control the active bleeding. The simple exposure of the pelvis, and, if need be, the proper enlargement of the pyelotomy into the parenchyma in cases of large stone, has much to commend it. I imagine this change has followed

the making of earlier diagnoses and, therefore, the removal of smaller calculi. This has been recently brought home to me in reviewing my teaching slides, and finding those of twenty and twenty-five years ago demonstrating conditions we rarely see today, all picturing much grosser surgical conditions. The closure of such an incision (pyelotomy) had best be left to nature, and unless unusually large, no sutures are used and no foreign material introduced, even ties, for I coagulate with electricity all bleeding points. If stitching be necessary, we use 000 and 0000 plain catgut and keep it entirely outside of the urinary passageway.

In ureteral calculus two things stand out: First, the simplicity and ease of ureterolithotomy in the upper two-thirds of the ureter; and I am quite positive and adamant in my preference for surgery as against instrumental efforts in such high ureteral calculi. Second, in the lower third of the ureter the picture changes, and instrumental manipulation is the first choice, but only under quite limited and strict rules for the game. We were joking only a few weeks back about our apparent proficiency in cystoscopic removal of low ureteral stones, and it started an analysis as to why we were so successful that we were listing a stone's *removal* almost as casually as though it were the appendix. We use the Howard corkscrew and the Johnson basket, being sure that each instrument is in perfect condition, especially the latter. We demand hospitalization and operating room surroundings. But probably the most important of all is the routine use of spinal anesthesia. I want the complete anesthesia and the perfect relaxation that it produces, and I believe a fair proportion of our success is due to its consistent use. Too often I feel we mistake analgesia for anesthesia in lots of our work, and in these cases I want the complete relaxation of all muscular activity that spinal anesthesia gives. I strive for that condition delightfully expressed by Jonesco as "abdominal silence" and "postmortem relaxation."

Prevention: As we approach a better understanding of the cause of stone, we naturally look for a better ability to control its occurrence. Let me outline briefly what our knowledge allows us to demand today: First, a prompt stone analysis; and we need improvement in this problem. There is rarely a truly pure stone, and when 90 per cent of a stone is of one salt, it should be considered pure for that alone. Recent chemical testing that has been advanced is too refined, perhaps too delicate, for certainly, unless a distinctly laminated calculus is present (and I am dealing principally with the small calculi where such is rare), one

cannot expect acid and alkaline salts to be alternately deposited; yet such a report is quite within reason with a recently published technique. If uric acid is the salt, let me urge a careful metabolic study, looking for the as yet undisclosed secret, and the giving to the patient of citro-carbonate, or a similar drug, to find the dose that will raise the urinary pH to 6.0 and keep it thereabouts. The oxalate stone is likewise a difficult problem, where to me dietary regulation is a poor crutch to depend upon, and where moderate alkalization may be tried. But I believe that in both of these salts the clearing up of all focal infections and the regular ingestion of at least 2,000 cc. of water daily are paramount. The calcium phosphate stone makers are to be studied to insure a well balanced diet, and are to be especially tested for hyperparathyroidism, and if the latter is positive, or even suggestive, exploration of the neck is urged. The taking of large quantities of water daily is perhaps the surest answer to our question of prevention, for given a dilute urine, there is little likelihood of sufficient concentration for any salt to be deposited as crystals, whether there be a nidus or not.

I believe we have a much better control today than even a decade ago, and probably a much more coöperative group of patients; but there is yet a great deal of work to be done, with, let us hope, a constant clarification of the problem and its complicated pathologic state.

CONCLUSIONS

Certain axiomatic statements can now be made in regard to calculogenesis. In this brief paper we have touched upon the five general theories of stone's formation, avitaminosis A, hyperparathyroidism, infection, colloidal imbalance and stasis, and none gives us a truly complete answer. Stone is now considered only a symptom in a very much broadened problem, and the answer is not so simple. We want, and must have, a common denominator for stone's origin, something which will act as a nidus to which the earliest crystal (be it what it may) can be attached; and for this we must go back beyond the occurrence of a visible calculus. As contributory factors we now know, not only that certain metabolic, dietary, infectious and pathologic conditions can produce the renal damage, but that, with such, also must occur the hyperexcretion of certain urinary salts, actually in supersaturation, verging on precipitation; and when these two conditions meet in the renal calyx, crystals are deposited, to grow into a primary renal calculus.

EXPERIENCE WITH ELECTRIC CONVULSIVE THERAPY IN VARIOUS TYPES OF PSYCHIATRIC PATIENTS*

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THIS presentation will deal with the clinical aspects of electric convulsive therapy. Realizing that the therapeutic possibilities of all shock methods are still limited, I shall discuss what types of psychiatric patients benefit from the treatment, and how optimal results can be obtained. The conclusions are based on various groups of psychiatric patients from two different hospitals. One series of 570 patients treated in the Psychiatric Institute, consists of voluntarily admitted patients and thus represents material seen in most research centers throughout the country. The second and larger group of almost 1200 patients from the Pilgrim State Hospital represents typical institutional material. The different results in two groups with different material treated by the same physician confirmed the view recently expressed by Dr. Lewis¹ that one of the main reasons for discordance in reports on shock therapy is the difference in material. It will be shown that an equally important reason for lack of agreement can be found in differences in the intensity of treatment.

Only a few questions of procedure will be discussed. It is still not generally understood that a convulsion is necessary for results. At the Psychiatric Institute a group of patients was treated by non-convulsive treatments alone.² There were no recoveries, but when the same patients, later on, were treated with generalized seizures, a fair number of them recovered. That convulsions are necessary was confirmed by several other studies. It is misleading when reports include petit mal responses in the total number of treatments given. For all practical purposes they are just as much failures as are metrazol injections without convulsive response. They can be avoided by giving a sufficiently strong current.

* Read April 11, 1944 before the Section of Neurology and Psychiatry of The New York Academy of Medicine.

We apply 100 volts for .15 seconds even with the first application. Some workers always give the highest amount of current obtainable with their machine. Animal experiments have proved the safety range of the method to be wide as far as the amount of current is concerned.³ A useful procedure is to apply a second stimulus with higher voltage if the first stimulus did not lead to an immediate convulsion. Waiting for the chance that mere unconsciousness may yet be followed by a delayed generalized seizure makes failures unavoidable and the application must then be repeated in a patient who is already weakened. While non-convulsive responses are not infrequently accompanied by respiratory and vasomotor distress and are sometimes followed by especially long periods of confusion, application of several stimuli immediately following each other has no untoward effect; nor does it increase the strength of the convulsion which depends exclusively upon the patient's muscular development.

A sufficiently strong current also permits the therapist to be generous with sedatives where they are needed. Agitated patients should be given sedatives because psychotic exhaustion increases the danger of collapse, and continuous baths, sometimes ordered instead of sedatives, are a considerable strain on the cardiovascular system. Sedatives like hyoscin do not increase the convulsive threshold at all, but even those used as anticonvulsants have little influence on the threshold even in toxic doses, as shown in studies with bromides and barbiturates.⁴ Only dilantin has a definite anticonvulsive effect. There is also no objection to the use of sodium amytal by mouth in patients who are restless after the treatment. In the more serious instances of postconvulsive excitements or furor-reactions, sodium amytal given intravenously⁵ is the treatment of choice. Since these reactions are rare, we limit this procedure to those patients who in the first treatment offered difficulties.

The problem most frequently interfering with the proper and effective progress of a course of electric convulsive therapy is presented by the organic mental symptoms occurring after a certain number of convulsions. All patients show early an impairment of memory as well as emotional disturbances, but there are also more dramatic organic reactions which are usually described as confusional states, but which are sometimes taken as reactivation of the psychosis, or as shifting from one type of psychosis to another. Careful psychiatric interviews of these patients reveal that acute psychotic pictures in patients who were quiet

and unproductive prior to treatment, do not represent an aggravation of their illness but a transient organic psychotic reaction to the treatment. Korsakoff pictures, acute hallucinosis and delirium are common. Like other symptomatic psychoses they invariably clear up within one or two weeks after the last convulsion. Misinterpreted as aggravation of the patient's original psychosis, they often lead to premature discontinuation of treatment. Likewise, treatment is often unnecessarily continued because the patient still offers symptoms which actually are no longer the expression of his original illness, but organic mental changes which will disappear only after termination of treatment.

These organic reactions are certainly the most unpleasant side-effect in electric convulsive therapy. In hospitals, though, they should not interfere with the progress of the treatment; in ambulatory patients they are a serious hindrance to intense treatment.

The complications of electric convulsive therapy, as well as the questions of contraindications, were discussed in another paper from the Psychiatric Institute at the last meeting of this section.⁶ I shall, therefore, limit myself to the remark that fatalities did not occur in my large material, but that I experienced instances of momentary cardiovascular and respiratory distress often enough to remain always conscious of the fact that the method is not without danger. Its indiscriminate use should be discouraged, especially by those who wish to prevent a method from falling into disrepute which proved to be valuable in various types of patients for whom no treatment was available in the past.

Conclusions regarding the possibilities and limitations of any therapeutic method are hampered by shortcomings of our psychiatric classification. Two patients with the same diagnosis can, in clinical appearance as well as in prognosis, be very different. Since it would be unjustified to delay the evaluation of a new therapeutic approach until psychiatric material is divided into better defined groups, a statistical study was limited to groups of clear-cut cases of the various psychoses. They were more easily found among the institutional material from which the figures demonstrated in this discussion are taken. Institutional material contains the greatest number of outspoken cases on the diagnosis of which psychiatrists of different schools would agree. Since many mild cases in patients who never see a psychiatrist, or are treated in clinics or open psychiatric hospitals, are automatically excluded, institutional material is not a selected group with a particularly good prognosis. It represents,

however, that group of psychotic patients which responds best to shock therapy.

The effectiveness of electric convulsive therapy is the least doubted in the manic-depressive psychosis. A depression can be cut short at any time with four to eight treatments. No greater number of treatments is necessary in deeply psychotic than in very mild cases. Here we come across a fact valid for all psychotics: The greater the loss of contact with reality the better the treatment prognosis. The figures for remissions in most reports on depressions vary between 80 and 90 per cent. In the manic phase results were discouraging as long as treatment was applied in the same way as in depressions; they are as good as in depressions if two or even three treatments are applied on the same day. This was well illustrated by a patient who had needed eighteen treatments in a severe manic excitement and who, two years later, in an equally severe manic state, cleared up under four convulsions given within 24 hours.

Electric convulsive therapy does not prevent future attacks of a manic-depressive psychosis. But patient and relatives usually consider it a great advance that we are able to cut short at will the suffering and suicidal dangers of a depression, or the implications of a manic excitement. The method fails in cyclothymic patients who continuously oscillate from one phase of the manic-depressive psychosis to the other.

In involutional melancholia results are fully as convincing as in other depressions. They are often more spectacular because, contrary to manic-depressives, involuntions can remain psychotic for years. It is interesting that several patients with psychoses of three or four years' duration did not need any more treatments than those with short depressions.

Results in the paranoid type of involutional psychosis are less favorable and not at all comparable to those obtained in pure depressions. The outcome in the paranoid group depends largely on the duration of illness, as it does in schizophrenia. Eight treatments as given in depressions, are insufficient. Now that we apply twenty, the same number as in schizophrenia, results are more satisfactory, but still do not reach half the number of remissions seen in depressions.

In view of these and other experiences in shock therapy, exact psychiatric diagnosing acquires new importance because it determines our therapeutic planning. Table I exemplifies the results obtainable in the affective disorders. The cases represented in this table were evaluated

TABLE I
RESULTS IN 200 CASES OF THE AFFECTIVE DISORDERS*

| | Total | Recovered and Much Improved | Improved | Unimproved |
|----------------------------|-------|--------------------------------|-----------|------------|
| Manic-depress. (depressed) | 60 | 52 (86.6%) | 4 (6.7%) | 4 (6.7%) |
| Manic-depress. (manic) | 32 | 27 (84.4%) | 3 (9.4%) | 2 (6.2%) |
| Involucional Melancholia | 76 | 66 (86.9%) | 8 (10.5%) | 2 (2.6%) |
| Involucional Paranoid | 32 | 14 (43.7%) | 8 (25%) | 10 (31.3%) |
| Total | 200 | 159 | 23 | 18 |

TABLE II
RESULTS IN 275 CASES OF SCHIZOPHRENIA*

| Duration | Total | Recovered and Much Improved | Improved | Unimproved |
|---------------------------------------|-------|--------------------------------|------------|------------|
| Less than 6 months | 60 | 41 (68.3%) | 13 (21.7%) | 6 (10%) |
| 6 months to 2 years | 82 | 34 (41.5%) | 24 (29.3%) | 24 (29.3%) |
| More than 2 years | 87 | 8 (9.2%) | 36 (41.4%) | 43 (49.4%) |
| Old cases with previous remissions | 46 | 26 (56.5%) | 10 (21.7%) | 10 (21.7%) |
| Total | 275 | 109 | 83 | 83 |

* Institutional material treated in the Pilgrim State Hospital, Brentwood, L. I. (from L. B. Kalinowsky, *Arch. Neurol. & Psychiat.*, 1943, 90:652.)

not by the therapist but by the staff of the State Hospital. A review of the failures among the depressions showed that some had schizoid features and might belong to the schizophrenic group. Likewise unfavorable are patients with severe hypochondriacal ideas. Finally, psychoneurotic admixture accounts for a number of incomplete remissions. It is mentionable that psychotherapy was not given to these patients who only had the usual State Hospital care. This is interesting in view of the similarity between the institutional figures and those given in a follow-up of my patients at the Psychiatric Institute⁷ where most patients receive at least some psychotherapy. This suggests the conclusion that psychotherapy, as desirable as it is, cannot be considered

indispensable for results with shock therapy as far as the major psychoses are concerned.

The good results in the affective disorders have overshadowed the much more limited therapeutic possibilities in schizophrenia. Yet, Cerletti and Bini devised the method for—and for a long time applied it exclusively to—the treatment of schizophrenia. When we discuss and recommend electric convulsive treatment in schizophrenia it is with the full realization that results are still limited with any of the shock methods. This, however, should not discourage their use as long as no better method is available. The psychological approach which would be available anyway only to very few patients, fails especially in those schizophrenics who respond best to shock therapy, viz., the least accessible patients who have the least contact with the outer world. The experiment offered by treating patients in the two types of hospitals showed convincingly the differences in prognosis and results of various types of schizophrenics. The group of voluntarily admitted, not acutely psychotic patients in the Psychiatric Institute, rich in borderline schizophrenics, offered poor and unconvincing results. The institutional material showed figures which were considerably higher than any comparative figures for spontaneous remissions. Institutional material permits the best comparison because it necessarily consists of patients with pronounced symptoms and a large group will have roughly the same composition in most institutions. It is neither surprising nor an objection to treatment that favorable and unfavorable prognostic factors are the same for the treatment prognosis as for spontaneous remissions. As in many other fields of medicine, we cannot expect to achieve more than to bring to a standstill an illness which is not altogether hopeless. As scientists we will have to ask for a final proof whether or not the successfully treated schizophrenics would have recovered anyway at some later time. As physicians we will apply treatment when we can hope to make the patient symptom-free at a given time. Results show that this can be done in a fair number of schizophrenics (Table II).

The most striking fact is the importance of the duration of illness. The hopelessness in cases of more than two years' duration makes early diagnosis and early treatment imperative. A prognostic factor of even greater practical importance is the type of onset, whether acute or insidious. In about 75 per cent of the patients listed as remissions, the onset was acute. On the other hand, cases of insidious onset and course, what-

ever the subtype, represent the majority of failures. A schizoid personality will not be influenced by the treatment. Therefore, extension of the concept of schizophrenia to such borderline cases would not falsify results to the better.

A follow-up of 111 of the patients paroled in the group shown in Table II revealed that within 6 months to 3 years only thirteen had to be returned, several of whom were again treated and paroled. It is felt that such figures justify treatment for the State and certainly for the individual patient and his family, although time does not yet permit to answer the question of a final cure in schizophrenics.

It is generally overlooked that Cerletti,⁸ when he introduced electric convulsive therapy as a treatment for schizophrenia, gave fifteen to forty convulsions as the necessary number. Convulsive treatment is very often inadequately applied. Like insulin, it requires a long course of applications. Electric convulsive therapy in schizophrenics is successful only if twenty or more treatments are given. Discontinuation of treatment when the patient shows the first clinical improvement, leads necessarily to failure. I had lasting results in a good number of schizophrenics who, elsewhere, had been discharged after an inadequate number of treatments and relapsed after weeks. A study of figures published by Malzberg⁹ for the Department of Mental Hygiene suggests the conclusion that the ratio between results in hospitals with similar material, some applying routinely twenty, others often less than ten treatments, was 5:2 in favor of the ones using intense treatment. On the other hand, the figures presented here practically repeat those given by other workers in convulsive therapy who applied twenty and more treatments. They also equal insulin figures as well as those of a recent statistical work by Braunmuehl for combined insulin and convulsive treatment.

Different indications for insulin and convulsive therapy are not yet established. Most statements made to this effect were not borne out by our experience. For instance, the statement that convulsive therapy has its best results in catatonic stupors is true only for the symptomatic breaking-up of the stupor but not regarding the final outcome which, like in insulin treatment, is less favorable in catatonic stupors than it is in paranoids. The same was recently reported by Neymann.¹⁰ Catatonic excitements had the best outcome; paranoids follow; poorest results were seen in hebephrenics. There were no patients of any type who showed a better response when shifted from one method to the other

provided they had received adequate treatment with the first method. A systematic comparison under controlled conditions between electric convulsive therapy and insulin, both applied adequately by competent workers, is unfortunately not yet available.

One special application of electric convulsive therapy in schizophrenia should be mentioned because of its practical importance. The change in the behavior of patients after as few as three or four treatments make electric convulsive therapy especially suitable for short, purely symptomatic treatment in chronic cases where no final remissions can be obtained. A maintenance treatment of one or two weekly, bi-weekly or even monthly treatments will keep the patient on a higher level. This appears to be one of the main tasks for ambulatory electric convulsive therapy. Many patients could be kept outside the institutions if psychiatrists would limit themselves in such cases to occasional symptomatic applications.

A group to which electric convulsive therapy seems to be widely applied is represented by the psychoneuroses. Here, our own results are quite unsatisfactory. Published reports based upon small series are contradictory. The results in neurotics are comparable neither in type nor in degree to those in psychotics. The disappearance of symptoms after four convulsions, so constant in the most different psychotic syndromes, is not seen in neurotics with the exception of the so-called psychoneurotic depressions; they can be successfully treated as far as the depression is concerned, although the patient's neurotic attitude remains unchanged. Anxiety states and conversion symptoms show little lasting benefit even from a long course of electric convulsive therapy. Neurotics often show an unpleasant reaction to the memory difficulties and organic character changes which frighten some of these patients severely. Neymann,¹¹ therefore, warns against the use of electric convulsive treatment in neurotics. In our experience favorable responses occur occasionally mainly in the obsessive-compulsive group, and it is interesting to speculate on the relation of such cases to schizophrenia. A symptomatic use of electric convulsive therapy can be made to relieve tension states with two or three treatments in order to make patients more accessible to psychotherapy. Selinski¹² reported first on this use which appears to utilize the organic affective blurring; it often breaks down the patient's resistance in a similar way as does sodium amytal in the narcosuggestive treatment

reported here by Hoch.¹³ The organic reaction of electric convulsive therapy can be used for various purposes, and it might be mentioned that I recently relieved a morphine addict from withdrawal symptoms with such short treatment. But we must realize that this is a symptomatic effect quite different from the treatment effect in psychotics. It is felt that in non-psychotics the use of electric convulsive therapy has its place only in a few carefully selected cases.

It is only for completeness sake that we mention a few experiences in epileptics. There is a definite rise of convulsive threshold after the first one or two electrically produced convulsions; this suggested attempts to give epileptics a few artificial convulsions under controlled conditions as a temporary protection against spontaneous fits. Mentioning of such attempts,⁴ which succeeded in several cases, does not imply any therapeutic recommendation in a condition where anticonvulsive medication remains the treatment of choice. The only practical recommendation which can be given in the epilepsies, is the breaking up of clouded states. These usually end with one or two spontaneous convulsions. Given at will by electrical stimulation they will shorten these dangerous mental states in epileptics.

It is attempted in this paper to give a survey of work done with electric convulsive therapy. Six years of experience appear to have shown that electric convulsive therapy is a valuable therapeutic procedure. This applies mainly to those types of psychiatric patients which are the least susceptible to a psychological approach. Aside from the other prognostic signs for the various psychoses, it can be said that dramatic symptomatology and loss of contact with reality are factors favorable for a response to shock therapy; that psychoneurotic admixture in psychotics and a well preserved personality make patients usually unresponsive to shock treatment. The most striking results are achieved in the affective disorders. There is no reason for overenthusiasm in schizophrenia, but early and adequate treatment will lead to gratifying results also in schizophrenics. In all but a few types of psychoneurotics electric convulsive therapy has failed and psychotherapy remains the treatment of choice.

There is as yet much work to be done to determine scientifically the actual accomplishments of electric convulsive therapy compared to other methods of treatment. The practical results are encouraging enough to use it as a purely empirical therapeutic approach, with the

view of finding better understood and more effective methods in the future.

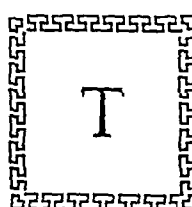
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THE PROBLEM OF SPECIALIZATION IN THE MEDICAL SERVICES OF THE REGULAR ARMY AND NAVY PRIOR TO THE PRESENT EMERGENCY*

LAWRENCE S. KUBIE

INTRODUCTION


THERE is a case to be made against intensive specialization in the medical services of the armed forces. The argument was admirably presented in 1923 by Capt. Carpenter† of the Navy. Capt. Carpenter reviewed the facilities for specialist training which existed at that time in both the Army and Navy medical schools, emphasizing the fact that within certain well-defined limits opportunities for specialist training were available in both. Capt. Carpenter quoted the opinions of many representatives of both services, and referred to the fact that "there are some senior medical officers of the Navy who are in favor of intensive specialization" although the majority dissented from this view. He pointed out that the scientific value of specialization is quite obvious, and that certain of its military disadvantages are equally obvious, such as the fact that the majority of military surgeons, whether Army or Navy, must be prepared to meet all emergencies in isolated posts. On the other hand there were other disadvantages, which might not occur at once to a civilian. Thus he quoted authorities who felt that for some time there had been an increasing and unwise tendency among younger medical officers to seek to specialize before they had acquired a broad base of varied experience in military medicine. He quoted others as emphasizing the danger that if there were a corps of specialists, the non-

*This study was completed nearly two years ago. At that time it was sent privately by the New York City Committee on Mental Hygiene to the Surgeons General of the Army and Navy, to certain other representatives of the medical services of our armed forces, to members of special committees of the Medical Section of the National Research Council, and to a few experienced leaders in medical administration and in medical education in this country. From these varied sources many illuminating suggestions have been received, of which full use has been made in this final version of the study. We are particularly happy to express our gratitude to Rear Admiral Ross T. McIntire (MC), Surgeon General of the U. S. Navy, and to Major General George F. Lull (MC), chief of the Personnel Service in the Office of the Surgeon General of the U. S. Army, for their helpful criticisms.

Finally we must acknowledge our special indebtedness to Mrs. P. A. Levene, for her meticulous care in compiling and checking the data on which this study is based.

† Carpenter, N., Captain, MC USN. The Military Surgeon as a Specialist, *U. S. Nav. M. Bull.* 1923, 18:177.

specialized medical officers might come to feel that it was no longer necessary to keep up in these specialties. He raised the issue of whether it would not have an adverse effect on general morale if there were specialists who could not be sent out on routine duties, but only in groups on capital ships or to large naval installations; and whether this would not make for invidious distinctions in the matter of advancements in rank. He quoted Admiral Rossiter (then Commander and later Surgeon General) as saying, "I feel equally sure that it would be most detrimental to the efficiency of the corps should they give entire attention to these specialties, as we must have men who can go to sea as 'medical officers'; and to establish a group of shore-going or fancy-job men would be destructive of morale, as it would tend to develop a sea-going and a shore division of the corps, for which reason I believe most emphatically that they should not give their entire attention to their specialties, but must keep up with the other subjects required of a naval medical officer."

Finally Captain Carpenter emphasized the danger that young men trained as specialists at government expense might resign to go into "the more lucrative fields of civil life." In discussions of this problem with regular medical officers, one frequently encounters a tendency to bypass the essential issue by attacking the trend toward specialization in civilian practice as being motivated largely by mercenary purposes. Thus an outstanding leader in the ranks of military medicine wrote: "It must be admitted, in the final analysis, that these things (to wit: membership in specialty societies, and certification by National Boards) are largely commercial." Although anyone who is realistic must acknowledge that economic motives play a role in civilian specialization, it is equally obvious that it is the proper use and not merely the improper abuse of specialization in medicine which must be considered in relation to the welfare of the armed services. The advantages and disadvantages of intensive specialization cannot be judged only by the behavior of those who exploit specialization for mercenary purposes.

For there is also a case to be made for the wider use of specialists in the regular medical services of the armed forces. This case was argued briefly by one whose services during the last War are remembered by all. In 1920, Col. Salmon,* wrote as follows: "I imagine that there

* Salmon, Thos. W., Col., MC USA. *The Future of Psychiatry in the Army*. *Mil. Surgeon*, 1920, 47:200.

will be no dissent from the statement that the regular establishment needs to have the important specialties adequately represented at all times in its own personnel. If there were no other reason, the retention of young medical men who enjoy military life, but who would leave the service if not permitted to work along the lines of their special interests, would be sufficient, in the present shortage of medical officers. Unless special as well as general tasks in military medicine are systematically undertaken in peace, it will be useless to expect regular officers, who will occupy high administrative positions in war, to know how to use specialists to the best advantage. Hostility or at least skepticism will be their attitude if they are thrown into contact with those working in special fields with no previous association as a basis for mutual understanding and respect. It is equally important that specialists should know how to work in the army. Many a highly trained specialist from civilian life was less able to apply his skill to the actual problems of military medicine because he insisted upon conditions that could not possibly exist in a military organization."

This was the matured point of view of a specialist, who never in his civilian career had been narrowly specialized, who had exceptionally wide experience in coördinating the work of general practitioners and specialists in the problems of civilian medicine, and who saw service in our army throughout the years of the last war as chief of the psychiatric division.

It is the lesson of his experience which makes us realize the importance of discussing the problem of specialization now. Together with many other specialized activities, the psychiatric division which during the last war functioned under his leadership was discontinued soon after demobilization. Presumably this was due in part to the inevitable though short-sighted post-war cuts in congressional appropriations, and in part to the natural tendency of the Army to revert to its habitual attitude towards medical specialties as soon as the return of peace lessened the influence of civilian physicians in military medical councils. It would seem to be almost certain that unless steps are taken to forestall this, the same thing will follow the termination of this war. At present every relevant specialty is represented in the medical services of the armed forces with steadily increasing strength. As this is taking place, close working relationships are being established both between individual specialists and the "regulars," and between the Office of the Surgeon

General and the national specialty societies and certification boards. If this close coöperation is truly valuable to national defense, then it would seem wise for all concerned to take steps now to ensure its continuance after the war.

The two opposing arguments which were quoted from Captain Carpenter and Colonel Salmon make it evident that the role of the medical specialist in the armed forces presents many perplexing issues. It is by no means clear how closely it should parallel his position in civilian medicine. Before considering problems of policy, however, it is necessary to ascertain what have been both the official policies and the unofficial but traditional attitudes and practices which have determined the position of the medical specialist in the regular armed forces. In general, has specialization been encouraged or discouraged? What proportion of military physicians, if any, were customarily given an opportunity to develop an interest in any specialty? Of, these, how many were enabled to acquire complete mastery of their special fields? Or did the policies and traditions of the services limit all or most to partial and intermittent specialization? More specifically one would have to investigate the opportunities for special training, the types of medical duties, the proportion of the officer's life which he would have to devote to matters other than his special field, such as tours of general duty or administrative functions, and the original contributions in special fields which have been made by members of the medical services.*

These are questions of fact which cannot be answered fully in the midst of a war; because final answers would require a study of records in the offices of the Surgeons General of the Army and Navy, and a survey of the scientific biographies of an adequate unselected sampling of regular medical officers. Nevertheless, the questions must be asked now in the midst of war, or they may never be raised at all. Furthermore, an approximate answer to certain of these questions can be found by determining how many regular medical officers of the armed services were members of national specialty societies or were certified as diplomates of any specialty board at the end of 1938, that is before the present emergency brought increasing numbers of civilian specialists into the armed forces.

The first purpose of this communication will be to present this sta-

* For a brief sketch of the history of specialization in the Navy, see: Rossiter, P. S., Rear Adm., M.C., Surgeon General, U.S.N., *Specialism and Postgraduate Training in the Medical Department of the Navy. Mil. Surgeon*, 1936, 79:169.

tistical information. Subsequently, the concluding discussion will take up certain questions of general policy. To avoid any possible misinterpretation of the significance of the data to be presented, however, it must be stated at once that membership in national specialty societies and certification by specialty boards are only indirect indices of specialized professional proficiency. Mastery of a specialty is best shown through the type of special training, by the range and quality of clinical experience, by the amount of active teaching, and by the original contributions in the field. After the war, it will be necessary to supplement and check the data reported here by gathering such information as this from official records.

DATA

These figures are compiled from information received from the secretaries of the several medical societies and medical specialty boards, checked against the information obtainable from the published transactions of the societies, the lists of names found in their special journals, the "Directory of the American Medical Association," and the 1939 "Directory of the American Board of Specialists." These figures are as correct as they can be without checking them further against questionnaires addressed to every member of each society and to every diplomate of each board. Furthermore, what errors may exist are not large enough to alter the general import of the data.

If we base our calculations on the fact that in 1938 there were about 180,000 physicians in the country, and about 1800 medical officers on active duty in the Army and Navy (or 1 per cent of the total), then military physicians might be expected to constitute something in the neighborhood of 1 per cent of the total membership of each specialty society, and 1 per cent of the diplomates of each specialty board.

Of course, such statistical expectations have only an approximate significance. Many variable factors influence the relative proportion of specialists to general practitioners in different communities, different climates, and in different occupational hazards. Such over-all percentages are only a convenient measuring rod with which to compare the representation of civilian medicine and of the medical services of the regular armed forces in the various specialties before the present emergency arose.

with no representation in dermatology, gastroenterology, proctology, neurosurgery, anesthesiology, pharmacology and experimental therapeutics, physiology, experimental pathology, neurology, climatology, or physical therapy. Of the special subdivisions of surgery, there was statistically expected representation in orthopedic and thoracic surgery only, and in these from the Army alone.

If one totals the data on membership in national specialty societies, omitting the four special cases referred to under paragraph 4, page 501, one finds that the statistical expectancy of representation from the armed services is 156. The actual total membership of regular medical officers of the Army and Navy is 59. Or, to put it another way, the armed services in 1939 were represented in national specialty societies about one-third as frequently in relation to their total numbers as were civilian physicians.*

7. Among the diplomates of specialty boards, one finds no representation from the armed forces in five (anesthesiology, dermatology, syphilology, orthopedic surgery, and urology); less than the statistically expected representation in psychiatry and surgery; and statistically expected representation in internal medicine, ophthalmology, otolaryngology, and radiology.

8. In 1939, approximately 8 per cent of the physicians of the country were diplomates of some board. In the same year about 6 per cent of all regular Army and Navy physicians were certified. For the country as a whole, approximately 70 per cent of all diplomates were certified in some specialty *other than general medicine or surgery*. Among the diplomates from the regular armed services, however, about 54 per cent were certified in some specialty other than general medicine or surgery, and of this 54 per cent, three-quarters were certified in ophthalmology or otolaryngology. This concentration of diplomates in these two fields is perplexing.

DISCUSSION

As has already been pointed out, membership in national specialty organizations is only one of several ways in which a man may manifest

*The question should be asked whether our national specialty societies have been fully alive to their responsibilities—whether through the years of peace they have sought to maintain a close liaison with the offices of the Surgeons General, and whether they have impressed on their memberships the importance of being adequately represented in the ranks of military medicine, in order that they should be prepared to make their special contributions to our national strength. Certainly the Specialists' Reserve Corps, the development of which was undertaken by the Navy, should be encouraged and supported by active campaigns in every national specialty society.

his proficiency in a specialty. Nor is it the best indication. Moreover, membership in a few of the national societies is based upon membership in local sections, to which military medical officers may not be eligible because of their relatively nomadic existence. (The American Urological Association has recently altered its rules so as to exempt military medical officers from this requirement.) Again some national societies require that the physician must practice the particular specialty alone; which in turn may automatically exclude otherwise qualified military medical officers.

In the course of time, certification will probably become a better indication of specialized competence, but in 1938 the principle of certification was still young; and even now not every qualified physician, whether civilian or military, submits to these examinations.

We are left therefore, with facts which are only partially informative, but which indicate that further investigation of the problem is desirable. In the meantime it is reasonable to ask how it happens that among the specialties (as opposed to general medicine or surgery, and excluding public health and tropical medicine as special cases), regular medical officers from the armed forces were represented as fully as their civilian colleagues in national specialty societies and among the diplomates of specialty boards only in the fields of ophthalmology, otolaryngology, and to a lesser extent in thoracic and orthopedic surgery.

Furthermore, since we are seeking evidence of specialization, it is important to emphasize the fact that membership in the American College of Physicians or in the American College of Surgeons, or certification by the American Board of Internal Medicine, while important as indication of a high level of general professional excellence, is not an indication of specialization. Indeed it might be argued that it might be well to require that every physician in the armed forces who is not trained as a specialist in some particular field should qualify as a member of the American College of Physicians or Surgeons; and that any such physician should be certified either by the American Board of Internal Medicine or by the American Board of Surgery, unless he is certified by some other specialty board.

The reason for this is presented in a letter from the Surgeon General of the Navy. He points out that in war as in peace, the physician in the armed services functions under more varied circumstances than those which confront the civilian practitioner. Admiral McIntire goes on to

say that the naval medical officer "must be qualified properly to treat any type of medical or surgical emergency which may arise when he is the one physician in a ship at sea; must be qualified to find the proper solutions for problems of hygiene, sanitation, and public health, arising in such an isolated community, which may within a short time pass from one extreme of weather to another; and must also be qualified as a medical administrator." (Personal communication December 5, 1942). These words describe with precision the challenge which confronts a large proportion of military physicians in the Army, the Navy, and the Air Forces. They indicate that the medical officer in such posts must be both administrator and general practitioner of exceptional ability.

No one can disagree with this description of the duties of the medical officer on isolated posts. But in the same communication the Surgeon General makes it clear that *every* medical officer is held to these requirements: i.e., although "Naval medical officers are encouraged to develop aptitude and experience in the various specialist fields. . . . the very nature of their basic specialty, however, (i.e., naval medicine) does not permit their concentrating upon one limited field." Similarly, Major General Lull writes: "When a young doctor enters the Medical Corps of the Army or Navy, there are certain things that he should make up his mind that he must sacrifice if he is to be successful. One of these is any high degree of medical specialization. He must become a specialist in military medicine instead. . . ." (Personal com., Oct. 30, 1942).

Thus both services operate on the assumption that every medical officer will meet the same challenges, must be ready to perform the same tasks, and must therefore go through the same mill. Every medical officer without exception must become a Jack of all the medical trades; yet somehow this is to be achieved without paying the penalty usually paid by the proverbial Jack of the adage. Somehow he must become in some degree a master of all; and the problem becomes the question of how this is to be achieved. Who is to teach him? Who is to establish practical standards of achievable proficiency in the many special fields he is supposed to master? And what happens to the man who may have exceptional aptitude in one field but who lacks the diffuse facility which makes possible the mastery of many? Has he no contribution to make in peace or in war to military medical science?

The entire problem is not unlike that which confronts the medical missionary in an isolated post; and if the military physician is to meet

those demands well it would seem that he must be trained as the best medical missionary is trained, through a series of internships in one special field after another, with interspersed periods of duty in which to test and perfect his mastery of each newly acquired special technique. In the end he will emerge from such a series of apprenticeships not a specialist in any one field but a superb general practitioner, equipped with a mastery of more of the special techniques of medicine and surgery than is possessed by the general practitioners of civilian medicine. Rarely, he may become an investigator; but more often he will be an applied medical scientist in the best sense of the word. One can only wish that the general practitioners of civilian medicine were held to the same high standards of broad and inclusive proficiency.

It is indeed clear that the military "general practitioner" and administrator is, as Admiral McIntire calls him, a "Specialist in Military Medicine" (*loc. cit.*), and that he will always be the backbone of military medicine. Nevertheless, it is necessary to consider whether the efficiency of this "Specialist in Military Medicine" and the efficiency and standards of the service as a whole could be raised to still higher levels by making more of a place in the medical services of the regular armed forces for the specialist as we know him in civilian medicine.

For instance, the succession of specialized apprenticeship, which has been described as the ideal program of postgraduate medical instruction for military needs, and which Admiral McIntire also refers to in his letter, requires the services of specialists; because in any field of medicine it is only the specialists whose teaching can keep pace with the advancing frontiers of knowledge.

Again, as Major General Lull points out (*loc. cit.*), in medical as in combatant troops the regular personnel constitutes the nucleus about which the organization must grow when the armed forces expand rapidly in an emergency. For this reason, among others, it would seem to be important to have the specialties fully represented in the ranks of medical "regulars", forming a cabinet of specialists around the Surgeons General. Human frailty must be given due consideration in determining such policies. One Surgeon General may understand the military uses and requirements of each specialty: whereas another, because of honest but obstinate prejudices, may overemphasize certain specialties and neglect others. Clearly the only way to balance out this uncertain human variable is by giving every relevant specialty a clearly recognized place

in the organization of military medicine.

In the last war, and again in the present struggle, the rapid mobilization of medical manpower demonstrated that if there is not full recognition of the importance of the medical specialties as necessary adjuvants to the military general practitioner, a tendency arises to waste highly trained personnel, and many avoidable misunderstandings and delays occur. Thus it took two years from the date of passage of the Selective Service Act of 1939 until a chief of a neuropsychiatric branch was appointed in the Office of the Surgeon General of the Army. Had such an officer been continuously at work over the years which have intervened since the last war, we would not have had to wait three years for the organization of psychiatric dispensaries to parallel the medical and surgical dispensaries in army camps, and four years for the recognition of the need for medically and psychiatrically trained social workers to function as clinical investigators.

Comparable problems have arisen with respect to plastic surgery. In this highly specialized field there are about 150 certified diplomates in this country, with almost no representation in the armed services prior to the emergency. Yet both in peace and in war the repair of mutilating injuries creates an incessant demand for the highly trained and experienced specialist. In civilian practice he is called upon by the orthopedic surgeon, by the neurosurgeon, by the pediatrician, and by all who deal with burns and industrial accidents. In peace as in war the armed services need him as a teacher, as a surgeon in difficult cases, and as a consultant in many others. He is needed also as a research worker to reproduce in the laboratory the mutilations caused by the changing weapons of war, and to experiment with the plastic restoration of destroyed tissues. Certainly it is inconceivable that we should offer surgical care to the soldier that is less skilled than the best which is available to the industrial worker.

In the absence of the true specialist in plastic surgery among the regular medical officers, one finds that there is inadequate appreciation of the need for plastic surgeons, and wholly inadequate plans for their use, their mobilization, and their emergency training; whereas the presence of such specialists will make it possible to assemble, organize, and train younger men during wartime emergencies. Through membership in national specialist societies the military regular who is a specialist in plastic surgery will be in touch with young plastic surgeons who are in

training all over the country, and with promising young general surgeons who under the stimulus of war can be developed into plastic surgeons for the needs of war by special courses of intensive supervised operative training. Clearly here again the Surgeon General's "cabinet" should at all times include a representative of this special field.

The same conclusions will be reached from a factual and objective study of the needs of the services, in peace and in war, with respect to almost all other medical and surgical specialties. The Offices of the Surgeons General should be composed of specialists, like the faculty of a medical school or the medical board of a teaching hospital.

The fact that a medical officer on an isolated post or ship must be prepared to meet all medical emergencies as best he may, is no more incompatible with the co-existence of the military specialist than is the co-existence of the country doctor and the specialist in civilian practice. As a matter of fact the armed services have approximated this very plan in the fields of tropical medicine and of sanitation. Our argument is essentially that similar considerations are applicable to all other specialties.

Innumerable examples could be given of the long delays which the existing system has caused in the appropriate use of medical men of all ranks as they were drawn from civilian medicine into the military forces. These delays cannot be explained away as due to a wise and wholesome policy of broad initiation into military life, because they have lasted long beyond any reasonable period of indoctrination. Nor should such delays be viewed indulgently as an unavoidable result of the speed with which the military organizations had to grow, because they occurred most seriously during the relatively leisurely year before Pearl Harbor.

On the other hand one can understand readily that there should be a natural tendency to continue in war the policies with which the services are already familiar in peace. It was quite inevitable therefore that at first there should be an effort to make of every incoming civilian doctor a military general practitioner. As the months and years of war have passed, this tendency has lessened, but in neither the last war nor in this has the basic policy been formally abandoned. The specialist is still not sure that he will be used in his own specialty, even to the extent that his specialty is needed in the medical work of the armed forces; and the old policy is still defended long after it has practically broken

down through its sheer unworkability.

Another manifestation of this is found in some of the special service schools for the indoctrination of newly inducted civilian physicians. These usually make the error of attempting to train every medical officer for every possible task, instead of classifying the newly inducted physicians in accordance with their civilian experience and then training them with the least possible loss of time only for the specific tasks which await them. It should be taken for granted that this would not supplant the more general indoctrination of numerous military "general practitioners" for service in theaters of operation, in isolated posts, and the like. In a total war, however, in which large numbers of older specialists enter the services, a parallel system of specialized indoctrination would economize time, teaching personnel, and facilities. It is only because of the deeply ingrained tradition that every military physician must be ready to fill any post, that the pedagogically unsound and impracticable policy persists of attempting to cram the entire curriculum down every throat.

At times one wonders just how well this traditional policy works even in leisurely periods of peace. From friends in the regular services one hears disquieting things about many of the indoctrination and refresher courses which are given at the army and navy medical schools. Too often they seem to have been short and superficial, almost as though they were a formal gesture, or scaled down to the level of the physician who chose military service as a refuge, as some civilian physicians choose the state hospital service. One hears that the courses are rarely difficult, with little weeding out of the unfit through severe examinations, and with little recognition of superior ability through quick reward. Only in one or two fields do they provide an opportunity for original work. In so far as these criticisms, which have been voiced by regular medical officers, may be true (which the writer is not in a position to judge), one would seem to glimpse again the influence of a traditional reluctance to allow medical officers to become fully mature in special fields.

To these reflections one might well add a consideration of whether medical administration also should not be recognized as a military medical specialty, as is happening in civilian medicine. Major General Lull writes of "men who are listed as members of specialty societies and certificants of the various boards, who are now commanding large hos-

pitals or serving on staffs of commanding officers of task forces." This leads one to wonder whether making over a medical specialist of proved ability into an administrator of uncertain calibre is not a waste of specialized scientific knowledge which we can ill afford, particularly in times of emergency. The issue calls to mind the statement attributed to the younger Ostwald who, on his return from a visit to the scientific institutions and universities of this country said: "When the Americans discover a man who is superbly fitted for some kind of scientific work, they reward him with a position in which he can no longer pursue it." Ostwald was talking of American universities; but the challenge is equally appropriate when directed to the medical services of our armed forces, because of an apparent tendency both in peace and in war to place medical officers of outstanding scientific and professional abilities under the yoke of routine administrative responsibilities.

One can at least picture a way of using the specialist in the armed services which might be scientifically sounder and at the same time more practical than existing policies. The military physician knows the ways and needs of the army or navy. A military physician who was at the same time a specialist would know both the needs of the services and the scientific requirements of his specialty as well. Furthermore, through his membership in national specialty societies, through his attendance at their meetings, and through his knowledge of the literature he would also have a direct acquaintance with the personnel available in that field. It is clear that such knowledge as this could be used to expedite greatly the induction and the proper utilization of specialists during any period of rapid mobilization and expansion.

The arguments against intensive specialization in the armed services assembled by Captain Carpenter (*loc. cit.*) do not seem to be unanswerable. For instance, he quotes Admiral Rossiter as saying that he has never had difficulty in placing naval medical specialists in positions where they could use their specialties. Again, it would seem to be not impossible to reserve such training for those who had already achieved a broad general training. Nor would it seem difficult to avoid the danger of losing the specialists to "the more lucrative fields of civil life", if such training were offered only on the express condition that the officer undertakes to remain in the service either permanently or else for a specified minimum number of years. In short Captain Carpenter's points seem to be important considerations for which plans must be

carefully made, rather than insuperable obstacles which make it impossible for the armed services to benefit by the presence of fully matured specialists in their own ranks.

These are some of the many reasons why it seems appropriate to ask whether it is not necessary to supplement the highly trained corps of general practitioners of what Admiral McIntire so aptly calls the "specialty of military medicine" with a large number of medical specialists, in the civilian sense of the term. A further question may be raised whether this may not best be achieved by further developing the Army and Navy medical schools to serve as centers of research and of post-graduate instruction in all special fields, with exchange professorships with civilian medical schools, and with adequate appropriations for laboratories, research, and publication.

For as we have said, mastery of a specialty is inadequately indicated by membership in specialty societies, or by special diplomas or certificates. Such mastery is best indicated by the teaching which the physician does in that field, and by the original contributions which he makes to it. It takes time to teach, to make original contributions, and to write. If we are to have fully competent specialists in the medical ranks of the regular armed forces, the life of the regular medical officers must allow time which can be devoted to this kind of work. Otherwise, able men may never have an opportunity fully to utilize their abilities in their fields of special interest and training; and in the end this will be reflected in the calibre of the physicians who serve in the regular forces of our Army and Navy.

SUMMARY

Since the last World War, large general hospitals have been developed as part of the medical installations of the Army and Navy. Such hospitals require the use of specialists in increasing numbers. Consequently a tacit, partial and unofficial recognition has been given to the need for specialists in the medical services of the armed forces. Qualifications for military specialization have not been clearly indicated, nor correlated with the rigorous principles and standards of National Specialty Boards. Nor have the many problems attendant upon this development been worked out fully. It would seem to be essential, therefore, that as an outcome of this inevitable trend and of the experiences of the last war and of this one, certain careful objective investigations should

be undertaken as soon as possible by a joint board, to consist of regular medical officers from the services, of civilian specialists who have served in the armed forces during the war, and of representative leaders in medical education, hospital organization and medical-social administration from civilian life. Such an inquiry might well be launched before the end of the war, as its end is clearly approaching.

. In a peaceful democracy the impetus towards studies such as these becomes strong only during a period of wartime crisis. The investigations themselves cannot be concluded in such a period; but the need for them can be pointed out and they can be initiated, so that when the war is over the lessons learned during war will not be forgotten by the civilian medical profession as a whole, by national specialty societies, by national qualifying Boards, nor by the military themselves.

THE IMPORTANCE OF THE Rh FACTOR IN MENTAL DEFICIENCY

*A Preliminary Report**

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APPROXIMATELY 30 per cent of admissions to institutions for mental defectives cannot be classified etiologically on the basis of our present knowledge. This, so-called, undifferentiated group represents a distinct challenge for medical investigation. The recent discovery of the Rh factor¹ and the demonstration of its importance in producing a characteristic type of fetal injury, namely, erythroblastosis fetalis² may be of importance in this respect. The possible relationship of Rh iso-immunization and certain types of mental deficiency is best described by the following brief review.

Some years ago we reported the pathological changes in the brain of infants who had died as a result of icterus gravis.³ This pathological condition, known as Kernicterus, included widespread ganglion cell injury in the cerebral cortex, cerebellum, basal ganglia as well as other structures. Later, we reported the clinical picture of children who had recovered from icterus gravis but subsequently exhibited evidence of central nervous system injury. This included severe mental deficiency, extra-pyramidal spasticity and athetosis. An autopsy on one of these children confirmed the relationship of the cerebral changes originally described as Kernicterus and the above mentioned clinical picture.⁴ At that time the etiology of icterus gravis was unknown. Beginning with the clinical studies of Diamond, Blackfan and Baty,⁵ it was demonstrated that icterus gravis represented one manifestation of the syndrome erythroblastosis fetalis. In 1941, Levine and his co-workers^{2, 6, 7} clearly indicated the importance of Rh iso-immunization in the etiology of erythroblastosis fetalis. Since Kernicterus is found primarily in children with erythroblastosis, it would appear reasonably well established

* From the Southbury Training School, Southbury, Conn. Presented before the Pediatric Section of The New York Academy of Medicine on April 13, 1944.

that the pathogenesis of the cerebral changes in this condition was in some way related to the Rh factor. At present, therefore, one may justifiably implicate Rh iso-immunization as the etiological mechanism in individuals with the following characteristics: (1) mother, Rh negative; (2) patient, Rh positive; (3) neonatal history of erythroblastosis fetalis; (4) evidence of basal ganglion disease; (5) severe mental deficiency. However, if this syndrome were the only manifestation of Rh iso-immunization, it would play a very insignificant role in the over-all picture of mental deficiency. Thus, at the Southbury Training School for Mental Defectives only one child was admitted with all these characteristics, among 1200 total admissions. There are, however, certain observations that suggest that Rh iso-immunization may play an etiological role in cases where basal ganglion disease is not manifested, and where a history of neonatal erythroblastosis is not obtained. These observations are of two types. In certain of the autopsied cases showing Kernicterus, the clinical picture was not characteristic of erythroblastosis fetalis, in that the blood examination was not considered abnormal, and the jaundice was minimal. Also, we have recently encountered patients with typical familial and clinical histories of erythroblastosis fetalis whose neurological disorder was essentially that of cerebellar dysfunction rather than basal ganglion defect. Similar discrepancies have been recorded in the literature.^{3,4} On the basis of these considerations there exists the possibility that certain of the imbecile and idiot defectives, now so unsatisfactorily classified as undifferentiated, may be etilogically explained as probable results of Rh iso-immunization.

Fortunately, this hypothesis lends itself to investigative confirmation. In a random sampling one would expect to find from 13 to 15 per cent of individuals, Rh negative. If a significantly greater proportion of mothers of an unselected group of undifferentiated defectives were found to be Rh negative, it might reasonably be deduced that in at least a number of these defectives, the mechanism of Rh iso-immunization was of etiological importance. In a preliminary survey, the incidence of Rh negative mothers of an unselected group of undifferentiated mental defectives was found to be approximately 25 per cent. On the other hand, among an equal number of mothers of mongolians, diplegics, microcephalics, etc., the incidence of Rh negative blood was in the normally expected range of about 12 per cent. While the total

number examined to date (approximately 100) is too small to draw definite conclusions, the difference between the two groups is statistically significant. The results are of sufficient interest to warrant further study.

While the demonstration of an Rh negative mother of an Rh positive mental defective does not make the diagnosis of fetal central nervous system injury due to maternal Rh iso-immunization, it does indicate the group in which this is a distinct possibility. Further clinical study of a large group of this type, may eventually result in a clinical characterization for which the blood studies may have confirmatory value.

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BULLETIN OF
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OCTOBER 1944

RECENT EXPERIENCES WITH
PENICILLIN IN THE TREATMENT OF
SURGICAL INFECTIONS*

FRANK L. MELENEY

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THE Committee on Chemotherapy and Other Agents of the National Research Council has been given the authority by the War Production Board to direct the use of a certain part of the available penicillin for clinical investigation in civilian cases. During the past year the units studying the prevention of infection in accidental wounds and burns under the direction of the Subcommittee on Surgical Infections, have had the opportunity of using some of this penicillin in established surgical infections.

In the August 28, 1943, number of the *Jour. Amer. Med. Asso.*, Keefer and his associates on the Chemotherapy Committee¹ reported on the first 500 cases treated with penicillin. More recent reports have appeared covering smaller groups of cases by Dawson and Hobby,² Herrell,³ and Bloomfield, Rantz, and Kirby,⁴ but these papers did not distinguish medical from surgical infections. Lyons' excellent report of his experiences with returned wounded soldiers dealt with surgical

* Work done under contract with the Office of Scientific Research and Development. Presented with the consent of the Committee on Medical Research of the National Research Council at the Surgical Section of The New York Academy of Medicine April 7, 1944.

infections largely associated with compound fractures.⁵ He brought out some important fundamental principles in this type of chronic surgical infection. But there has not been any presentation of various types of surgical infections treated with penicillin as far as we know. Inasmuch as the units studying purely surgical infections have now submitted records of over 275 cases and these have been observed from a surgical viewpoint and a tentative appraisal has been made of penicillin with consideration given to the natural course of surgical infections, it seems timely to present a review of these cases as a preliminary report. Summary sheets have been approved by the Subcommittee on Surgical Infections and Burns of the National Research Council for a more detailed study of established surgical infections and their treatment by sulfonamides, penicillin, and other antibacterial substances. A more definite appraisal of these agents will be possible when these records are available from a large number of cases. In this paper we would like to point out some of the differences between medical and surgical infections, to call attention to the difficulty of appraising drugs in surgical infections, and to present a few illustrative cases.

Surgical infections differ from medical infections in the following important respects. (1) There is a local breakdown of tissue or enclosed purulent exudation which either has to be evacuated or absorbed and which may nullify the effect of any antibacterial agent. (2) Thrombosed blood vessels in the walls of these areas of tissue breakdown may prevent the inflow of antibacterial agents from the blood stream into the area of bacterial activity. (3) Surgical infections are frequently due to a mixture of organisms, especially contaminated accidental wounds and war wounds and particularly gas gangrene. (4) Being local, surgical infections permit the local as well as the general administration of drugs. (5) Repair occurs with scar tissue and not a restoration of the tissues to normal as with medical infections. (6) The relation of the time of drug administration and the surgical procedure to the onset of the infection is extremely important in surgical infections. Presumably the drug acts best if given early during the stage of cellulitis before there has been much tissue breakdown. The surgical procedure may do the most good and the least harm if delayed. Both may be necessary to control the infection.

The history of man's fight against infection has been a series of exaggerated roseate hopes followed by disillusionment but progress has

been made—step by step. Ever since bacteria were found to be the cause of infections, panaceas have been sought for and frequently acclaimed, aided and abetted by the lay press with or without the encouragement of the discoverer or chief advocates. The goals of the doctors combating infections should be (1) the prevention of the entrance and the establishment of bacteria within the human body and (2) the destruction or the nullification of the action of any bacteria already established in the body.

There are so many factors operating in any case of surgical infection that it is difficult to evaluate the use of drugs. We must be cautious and not be carried away by too great enthusiasm but view the problem objectively. However, a drug may be said to be effective in surgical infections if it (1) obviates surgery in a condition otherwise requiring incision, (2) permits a more limited surgical procedure than usual, (3) shortens the time of control of the infection, (4) permits primary closure after incision or (5) permits earlier secondary closure than usual.

The discoverers and proponents of penicillin have been conservative in their claims and have tried hard to evaluate it and find the best way to administer it. Fleming,^{6,7,8} Florey,^{9,10} Chain¹¹ and Garrod¹² deserve great credit for their painstaking conservatism in the development of the drug and the critical, scientific, logical methods that they have used to demonstrate its indications and its limitations. In this country its potential value to the war effort has led the War Production Board to maintain complete control of the supply and limit its use to the Army, the Navy, and accredited individuals under the Committee on Chemotherapy and Other Agents. From these cases of surgical infections treated by the surgical units the following data have been submitted—the diagnosis, the bacteriology, the method, amount and duration of drug therapy, the time relationship of drug treatment to the onset of infection and to the surgical procedure, if any. The results have been recorded as (1) excellent or brilliant with an almost immediate response (within 48 hours), (2) good—slower but definite benefit, (3) questionable, when the case might have done as well without the drug, and (4) no effect when the infection went its usual course.

Until more cases have become available and more details can be analyzed only the most obvious trends can be seen. Fully developed conclusions cannot be drawn.

PENICILLIN TABLE I—MARCH 1, 1944
ESTABLISHED SURGICAL INFECTIONS

| <i>Method Used</i> | <i>Total</i> | <i>Results</i> | | | |
|------------------------|--------------|-------------------|-------------------|---------------------|-------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Questionable</i> | <i>No Effect</i> |
| General only . . . | 144 | 55 (38.2%) | 40 (27.8%) | 22 (15.3%) | 27 (18.7%) |
| Local only . . . | 64 | 13 (20.3%) | 23 (36.0%) | 17 (26.6%) | 11 (17.2%) |
| Both local and general | 67 | 22 (32.9%) | 20 (29.9%) | 12 (17.9%) | 13 (19.4%) |
| TOTAL | 275 | 90 (32.7%) | 83 (30.2%) | 51 (18.5%) | 51 (18.5%) |
| Surgery | 155 | 48 (31.0%) | 51 (32.9%) | 31 (20.0%) | 25 (16.1%) |
| No surgery | 120 | 42 (35.0%) | 32 (26.6%) | 20 (16.7%) | 26 (21.7%) |

In surgical infections the opportunity is given for three methods of drug therapy, general, local, and combined. In Table I the 275 cases are divided into these three groups and the results recorded for each. For the most part the cases receiving general treatment gave some clinical evidence of systemic spread either of the bacteria themselves or their poisons. For that reason they were generally more serious than those receiving local treatment only. Those treated locally offered the opportunity for local application of the drug, in most instances after a surgical incision but at times following simple aspiration of a purulent collection. It is of interest that the sum total of favorable results are remarkably even in the three groups but the highest percentage of brilliant results occurred in those receiving general treatment only and the "excellent" outweighed the "good." While in the cases with only local treatment, the "good" outweighed the "excellent." This may be explained by the fact that in the "general" group there were many early cases in which the infection was in a stage of cellulitis while in the local group there had been a breakdown of tissue which took time to be evacuated or absorbed even after surgical incision. It is obvious that this table needs a careful breakdown and analysis before methods of administration can be compared one with another. Conclusions cannot be drawn from it.

Table I also reveals that 120 of these 275 cases, ordinarily classed as surgical infections, did not have a surgical incision. Aspiration was

PENICILLIN TABLE II

MARCH 1, 1944

| <i>Diagnoses</i> | <i>Totals</i> | <i>Results</i> | | | |
|---|---------------|------------------|-------------|---------------------|------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Questionable</i> | <i>No Effect</i> |
| Staphylococcus aureus septicemia, cryptogenic | 6 | 3 | 1 | 1 | 1 |
| With endocarditis | 6 | | | | 6 |
| With endocarditis (?) | 1 | 1 | | | |
| With acute osteomyelitis | 15 | 8 | 6 | 1 | |
| With suppurative arthritis | 2 | 2 | | | |
| With meningitis | 1 | | | | 1 |
| With brain abscess | 1 | 1 | | | |
| With multiple abscesses | 1 | | 1 | | |
| With third degree burn | 2 | 1 | | | 1 |
| With pemphigus | 1 | | | | 1 |
| With diabetes | 2 | | 1 | | 1 |
| With furunculosis | 3 | | 3 | | |
| With cellulitis of face | 2 | 2 | | | |
| With cavernous thrombosis (?) | 1 | 1 | | | |
| With cellulitis of chest wall | 1 | 1 | | | |
| With lung abscess | 2 | 1 | | | 1 |
| With empyema | 1 | 1 | | | |
| With patent ductus | 1 | 1 | | | |
| With pyonephritis | 2 | 2 | | | |
| Following hysterectomy | 1 | | 1 | | |
| TOTALS | 52 | 25 (48%) | 13 (25%) | 2 (4%) | 12 (23%) |
| Hemolytic streptococcus septicemia | 8 | 2 | 2 | | 4 |
| Non-hemolytic streptococcus septicemia | 1 | 1 | | | |
| Anaerobic streptococcus septicemia | 3 | 1 | | 1 | 1 |
| Staphylococcus albus septicemia | 1 | 1 | | | |
| TOTALS | 13 | 5 | 2 | 1 | 5 |

PENICILLIN TABLE III—MARCH 1, 1944

| <i>Other Main Diagnoses (I)</i> | <i>Total</i> | <i>Results</i> | | | |
|---|--------------|------------------|-------------|---------------------------|----------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Question- able</i> | <i>No Effect</i> |
| Chronic osteomyelitis | 39 | 6 | 15 | 10 | 8 |
| Acute osteomyelitis | 4 | 3 | 1 | | .. |
| Suppurative arthritis | 10 | 3 | 3 | 3 | 1 |
| Suppurative arthritis with osteo... .. | 3 | 2 | 1 | .. | .. |
| Compound fracture | 14 | 5 | 7 | 1 | 1 |
| Infected operative wound | 8 | 1 | 3 | 3 | 1 |
| Infected burn | 9 | 2 | 2 | 2 | 3 |
| Superficial abscess | 27 | 10 | 10 | 3 | 4 |
| Deep abscess | 5 | 1 | 2 | 2 | .. |
| Gas gangrene (Welchii)..... | 5 | 2 | | 3 | .. |
| Gas gangrene (Novyi) | 1 | 1 | .. | | .. |
| Gas gangrene (Serdellii) | 1 | .. | .. | .. | 1 |
| Empyema | 9 | 1 | .. | 4 | 4 |
| Lung abscess | 2 | .. | 1 | 1 | .. |
| Post-operative pneumonitis | 1 | .. | 1 | .. | .. |
| TOTAL | 138 | 37 | 46 | 32 | 23 |

done in many of these cases but no cutting. And yet the results in the four classifications are almost as good as in the cases which were operated upon. A detailed analysis however would show that these two groups are not comparable. The cases operated upon had the largest number of serious cases and in many of them treatment was instituted late while in the non-operated group treatment was frequently instituted early—in the stage of cellulitis before there was any indication for surgery. However in many of these cases drug treatment obviated what would otherwise have been necessary surgery.

Table II shows the cases of septicemia. Fifty-two of these were due to the hemolytic *Staphylococcus aureus* and the results indicate a favorable response in 73 per cent of cases. Of the twelve cases in which there was no effect six were demonstrated to have endocarditis and the other six may have had foci hardly approachable either by the drug

PENICILLIN TABLE IV—MARCH 1, 1944

| Other Main Diagnoses (II) | Total | Results | | | |
|-------------------------------------|-------|-----------|------|-------------------|--------------|
| | | Excellent | Good | Question- able | No Effect |
| Actinomycosis | 6 | 1 | 4 | 1 | .. |
| Ulcer of skin | 9 | 4 | 2 | 1 | 2 |
| Chronic undermining ulcer | 2 | | | 1 | 1 |
| Cellulitis of face | 3 | 2 | 1 | .. | .. |
| Cellulitis of neck | 6 | 2 | 2 | 2 | .. |
| Cellulitis of orbit | 4 | 3 | 1 | .. | .. |
| Carbuncle | 6 | 3 | 2 | 1 | .. |
| Furunculosis | 3 | | 3 | .. | .. |
| Penphigus | 1 | | | .. | 1 |
| Pyoderma | 2 | | | 2 | .. |
| Erysipeloid | 2 | 2 | | .. | .. |
| Peritonitis | 3 | .. | 2 | .. | 1 |
| Subphrenic abscess | 4 | .. | | 2 | 2 |
| Liver abscess | 3 | 2 | .. | 1 | .. |
| Pelvic thrombophlebitis | 2 | 2 | .. | .. | .. |
| TOTAL | 56 | 21 | 17 | 11 | 7 |

or by a surgical procedure. That almost half of these septicemias had a brilliant result and another quarter a frankly good result, strongly suggests that penicillin is meeting a real therapeutic need in a disease formerly producing a mortality of 80 per cent and which was not met by the sulfonamides. The results were not so good in the small series of hemolytic streptococcus septicemias where the table indicates a favorable outcome in only 50 per cent. However it should be noted that the smallness of this series is itself a triumph for the sulfonamides which have made hemolytic streptococcus septicemia a rare disease. This table obviously needs more detailed analysis.

Table III gives clinical diagnoses which permit certain groupings with their results. It is seen that the response in the cases of chronic osteomyelitis leave something to be desired. This group needs a more detailed analysis to bring out the reasons for success on the one hand

PENICILLIN TABLE V—MARCH 1, 1944

| <i>Miscellaneous Diagnoses</i> | <i>Total</i> | <i>Results</i> | | | |
|---|--------------|------------------|-------------|---------------------------|----------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Question- able</i> | <i>No Effect</i> |
| Brain abscess with osteo. skull. | 1 | | 1 | | |
| Meningitis, cav. sinusitis with osteo skull | 1 | | 1 | | |
| Meningitis from abscess face | 1 | | | | 1 |
| Mastoiditis | 2 | 1 | 1 | | |
| Bronchiectasis | 1 | 1 | | | |
| Gangrene of foot | 3 | 1 | | 2 | |
| Osteochondritis | 1 | | 1 | | |
| Infected skin graft | 1 | 1 | | | |
| Human bite | 2 | | 1 | | 1 |
| Ulcerative colitis | 1 | | | | 1 |
| T. B. sinus with secondary infection | 2 | | | 1 | 1 |
| TOTAL | 16 | | | | |

and failure on the other, the factors of duration of illness, extent of disease, necrosis of tissue, and nutritional depletion being of particular importance. The results are more favorable in acute osteomyelitis, suppurative arthritis, compound fractures, and in superficial abscesses.

The small group of gas gangrene cases requires careful study. The details have not been furnished in all of these cases, but certain things stand out. It must be constantly borne in mind that gas gangrene is almost always a polymicrobial disease with necrosis of tissue. One of the seven cases was due predominantly to *C. oedematiens*. The result was said to be excellent but amputation was deemed necessary. This was done through and not above the involved tissue. One was due primarily to *C. sordellii*. Although *welchii* was also present, there was no gas or necrosis of tissue—but a malignant edema; 50,000 units of penicillin every three hours had no effect, obviously not enough. In two of the Welch cases the result was called excellent but amputation was required. This classification seems faulty here because amputation can hardly be considered the result desired. In the three questionable cases the value of penicillin could not be determined with certainty. In one

PENICILLIN TABLE VI—MARCH 1, 1944

| Bacteria | Totals | Results | | | |
|---------------------------------|--------|-----------|------|--------------|-----------|
| | | Excellent | Good | Questionable | No Effect |
| Staphylococcus aureus | 121 | 47 | 44 | 15 | 15 |
| Hemolytic streptococcus ... | 13 | 4 | 4 | | 5 |
| Both S. A. and H. S. | 11 | 3 | 4 | 3 | 1 |
| Other mixtures | 85 | 19 | 18 | 24 | 24 |
| Anaerobic strept. | 3 | 1 | | 1 | 1 |
| Staphylococcus albus | 4 | 1 | | 3 | |
| Coagulase micrococci | 4 | 1 | 2 | | 1 |
| C. welchii (perfringens) ... | 2 | 1 | | 1 | |
| C. welchii sordellii | 1 | | | | 1 |
| C. novyi (edemetiens) ... | 1 | 1 | | | |
| C. welchii and Hem. strept. | 1 | 1 | | | |
| Non hemolytic strept..... | 1 | 1 | | | |
| E. coli | 2 | | 1 | | 1 |
| Pneumococcus | 3 | 2 | 1 | | |
| Actinomycosis | 5 | | 4 | 1 | |
| Erysipeloid (clinical) | 2 | 2 | | | |
| Non-hemolytic staphylococcus .. | 1 | 1 | | | |
| Unknown | 15 | 5 | 5 | 3 | 2 |
| TOTAL | 275 | 90 | 83 | 51 | 51 |

of these amputation was done. The favorable results in gas gangrene cases with penicillin reported from the combat zones have also for the most part been in cases where amputation was done. The accredited effect was obtained by continued use of the drug after amputation. It has been reported that penicillin permitted amputation through the diseased tissue, leaving some in, whereas without the drug, amputation to be successful had to be above the site of the disease. This would not seem to be a very clear cut demonstration of the value of the drug, leaving much to be desired. It would seem to be essential to explore other methods of combating this infection, and perhaps methods should be vigorously pursued of combating the associated organisms, particu-

PENICILLIN TABLE VII—MARCH 1, 1944

DOSAGE—GENERAL

Including those cases with general and with combined general and local treatment

| Units | Totals | Results | | | |
|------------------------------------|--------|-----------|------|---------------|-----------|
| | | Excellent | Good | Question-able | No Effect |
| Up to 250,000. | 37 | 8 | 7 | 7 | 15 |
| Over 250,000 up to 500,000. | 53 | 27 | 10 | 8 | 8 |
| Over 500,000 up to 750,000. | 29 | 6 | 15 | 3 | 5 |
| Over 750,000 up to 1 million. | 24 | 9 | 7 | 7 | 1 |
| Over 1 million. | 62 | 25 | 19 | 9 | 9 |
| Not stated. | 6 | 2 | 2 | 0 | 2 |
| TOTALS. | 211 | 77 | 60 | 34 | 40 |

DOSAGE—LOCAL

Including those cases with local and with combined general and local treatment

| Units | Totals | Results | | | |
|--------------------------------|--------|-----------|------|---------------|-----------|
| | | Excellent | Good | Question-able | No Effect |
| Up to 10,000. | 46 | 13 | 17 | 9 | 7 |
| Over 10,000 up to 20,000. | 10 | 2 | 3 | 2 | 3 |
| Over 20,000 up to 30,000. | 5 | 1 | 1 | 3 | .. |
| Over 30,000 up to 40,000. | 4 | 1 | 1 | 1 | 1 |
| Over 40,000 up to 50,000. | 5 | 2 | 1 | 2 | .. |
| Over 50,000. | 39 | 7 | 11 | 11 | 10 |
| Not stated. | 22 | 9 | 9 | 1 | 3 |
| TOTALS. | 131 | 35 | 43 | 29 | 24 |

larly the Gram-negative bacilli so often present, which frequently inactivate the penicillin.

Table IV lists smaller groups which are hardly susceptible of analysis but the general trend is favorable particularly in those cases which were superficial and approachable by local treatment or were in the stage of cellulitis when treatment began.

Table V lists miscellaneous cases of relatively minor importance.

Table VI indicates the bacteriology and three points seem to stand out. The first of these is the importance of knowing with certainty the bacterial etiology of all of these infections, for it is obvious that prognosis depends upon this knowledge. It is clear that highly favorable results may be expected in 75 per cent of the pure hemolytic *Staphylococcus aureus* cases but the response is less favorable in the hemolytic streptococcus infections and where there are mixtures of organisms. These cases must be further analyzed with respect to preceding treatment. Just which mixtures responded and which resisted may well bring out some interesting ideas regarding bacterial synergism and antagonism. While the cases of actinomycosis showed some initial success, time must be given for a final appraisal of this type of infection.

Dosage is shown in Table VII and it is at once apparent that less than a quarter of a million units systemically is frequently ineffective. It must be remembered however that in this group are those fulminating cases which died before adequate dosage could be given as well as those receiving inadequate dosage over a longer period of time. The results in the other groups show very similar percentages on the favorable side, namely 71 per cent, 72 per cent, 66 per cent, 71 per cent. However the dosage for general administration and the consideration of the intravenous versus the intramuscular route need detailed analysis. Lyons² has emphasized the need for larger doses in staphylococcal than in other types of infection, but in this series the pure staphylococcal group has done particularly well on relatively small doses—frequently 40,000 units have given brilliant results in serious cases. Of course, 80,000 units might have given a more comfortable margin and accomplished the results more quickly. It must be remembered that Lyons' cases were for the most part compound fractures where necrotic tissue and associated proteolytic organisms and lowered nutritional status were factors of major importance. It would seem reasonable in pure staphylococcal infections to start off with 80,000 to 100,000 units and in mixed infections to double this amount. Then, if the result is not satisfactory in 24 or 48 hours, these doses may be increased.

Local dosage of less than 10,000 units has been frequently favorable in well localized infection. It is obvious however that much more study must be given to the concentration, dosage, frequency of administration and the vehicle to be used for local administration.

Table VIII reveals that in the great majority of these cases sulfona-

PENICILLIN TABLE VIII—MARCH 1, 1944
PREVIOUS SULFONAMIDE TREATMENT

| | <i>Totals</i> | <i>Results</i> | | | |
|--|---------------|------------------|-------------|---------------------------|----------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Question- able</i> | <i>No Effect</i> |
| No previous treatment of any kind. . . . | 45 | 14 | 14 | 12 | 5 |
| Sulfadiazine | 171 | 58 | 53 | 25 | 35 |
| Sulfathiazole | 35 | 9 | 11 | 9 | 6 |
| Sulfanilamide | 11 | 6 | 4 | 1 | |
| Sulfamerizine | 2 | 1 | | 1 | |

ACCOMPANYING SULFONAMIDE TREATMENT

| | <i>Totals</i> | <i>Results</i> | | | |
|--|---------------|------------------|-------------|---------------------------|----------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Question- able</i> | <i>No Effect</i> |
| No accompanying drug treatment | 172 | 57 | 47 | 40 | 28 |
| Sulfadiazine | 34 | 10 | 5 | 4 | 15 |
| Sulfathiazole | 2 | | 1 | | 1 |
| Sulfanilamide | 2 | 1 | 1 | .. | .. |
| Sulfapyridine | 1 | | 1 | .. | . |
| Sulfamerizine | 1 | . | 1 | .. | .. |
| Sulfacetamide | 1 | | . | .. | 1 |

DURATION OF TREATMENT

| | <i>Totals</i> | <i>Results</i> | | | |
|-------------------------|---------------|------------------|-------------|---------------------------|----------------------|
| | | <i>Excellent</i> | <i>Good</i> | <i>Question- able</i> | <i>No Effect</i> |
| Up to 5 days | 41 | 10 | 8 | 12 | 11 |
| 6 to 10 days | 62 | 19 | 25 | 9 | 9 |
| 11 to 15 days | 47 | 16 | 12 | 10 | 9 |
| 16 to 20 days | 28 | 8 | 11 | 4 | 5 |
| Over 20 days | 31 | 9 | 10 | 10 | 2 |
| Not stated | 66 | 28 | 17 | 6 | 12 |
| TOTALS | 275 | 90 | 83 | 51 | 51 |

mides have been used previously without effect and the results have been just about as good in these cases as in those not previously treated by anything. In a certain number of cases, sulfonamides have been used along with the penicillin or subsequently if penicillin alone failed to control the infection. This synergism of the two drugs needs further study.

With regard to the duration of the treatment it would appear that a minimum of six days is advisable. In the shorter group are not only the fulminating cases but those in which treatment was terminated promptly following a prompt resolution of the process. It is obvious however in several of these cases that a wider margin of safety would have been preferable.

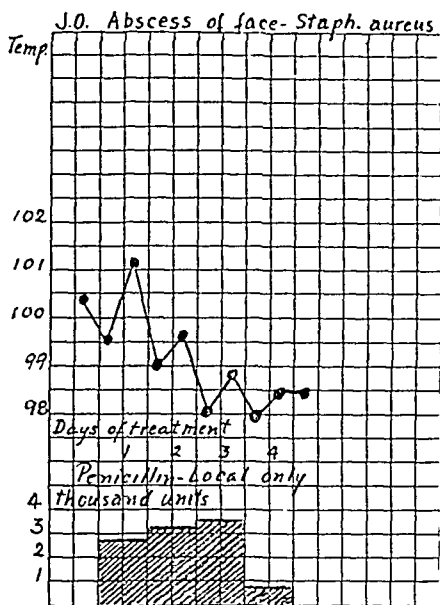
An analysis of the causes of failure or questionable results reveals two outstanding associated conditions, namely the presence of necrotic tissue and/or a mixture of organisms. A few cases were fulminating or the patients were moribund and treatment was obviously instituted too late. Occasionally organisms belonging to susceptible groups were found to be resistant to penicillin, but for the most part the failures were in cases of polymicrobial infections which included Gram-negative bacilli. Where hemolytic staphylococci and hemolytic streptococci were present together, the infection was often much more virulent than in pure infections with either of these organisms. Larger initial doses may be indicated in such cases. There are among these failures and questionable results many cases in which the cause of failure is not apparent—cases in which the organisms were susceptible and yet nothing happened. It will require a more careful study of the details of these cases before the cause for failure can be determined.

Certain of the individual cases bring out some interesting points and are therefore briefly abstracted. The temperature curves and dosage graphs are shown in the accompanying figures, page 530.

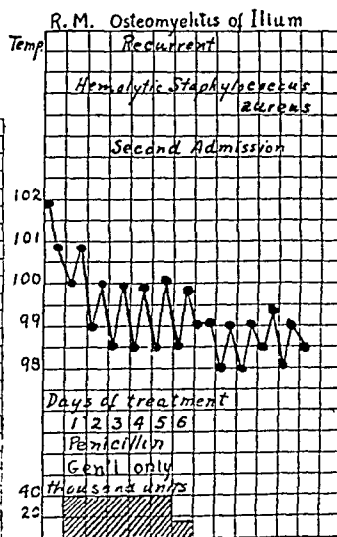
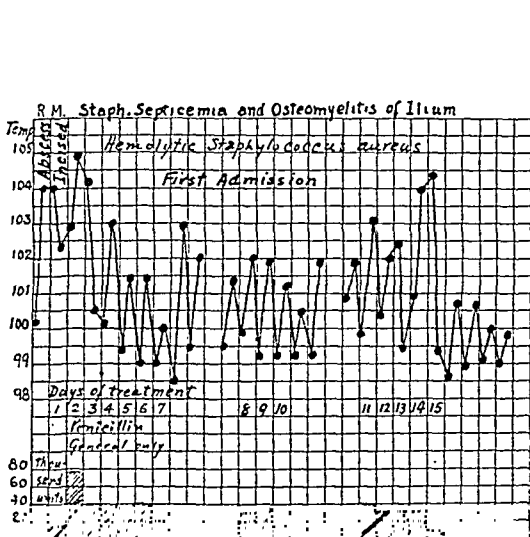
SUMMARY

1. A preliminary analysis has been made of 275 cases of surgical infections treated with penicillin by a group of surgeons* directing the

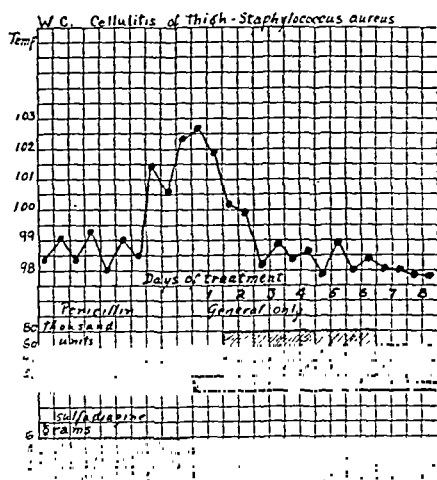
* Case records included in this summary have very kindly been sent in by Drs. Max Zininger and William Altemeier of Cincinnati, John Lockwood and William White of Philadelphia, Warfield Firor and Eleanor Bliss of Baltimore, Alton Ochsner, Guy Caldwell, and Maxwell Kepl of New Orleans, Roy McClure, Conrad Lam and John Hirshfeld of Detroit. The abstracts and temperature curves are from cases from the Presbyterian Hospital in New York under the supervision of Harold Harvey, George Humphreys, Robert Elliott and Frank Meleney. Acknowledgement is gratefully made herewith.



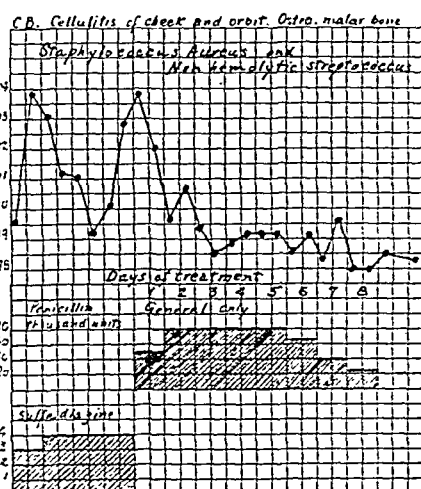
Case I: J. O. A girl of 17 with a history of two facial abscesses, incised and slow to heal, had a third and larger hemolytic *Staphylococcus aureus* abscess of the cheek, with swelling in the floor of the mouth. Local instillation only, of about 3000 units of penicillin once daily for three days resulted in prompt resolution of the process.



Case II: R. M. A boy of 15 with a hemolytic *Staphylococcus aureus* septicemia following a boil on the knee, a bruise of the hip, and an evening toss in a lake, failed to respond to sulfonamides or incision of an abscess over the ilium. The septicemia cleared with 40,000 units of intramuscular penicillin daily although metastases threatened to develop in the lungs. While the wounds healed, progressive destruction of the ilium occurred, and during convalescence an abscess developed on the inner surface of that bone. This however resolved without incision following a second short series of penicillin treatments. Thereafter symptoms completely subsided and have not recurred in over a year. Furthermore X-ray films reveal a regeneration of the bone.



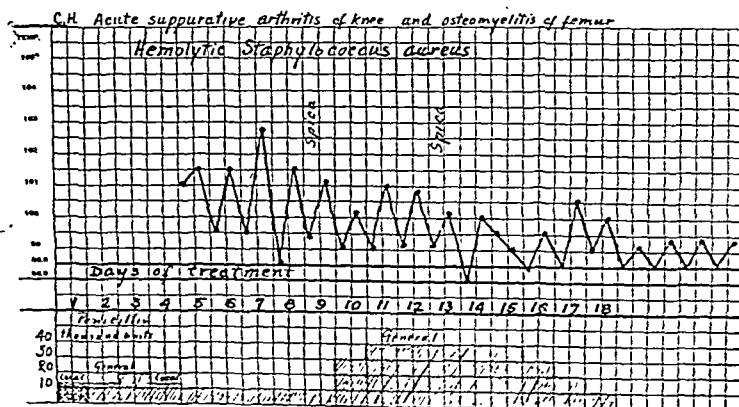
Case III



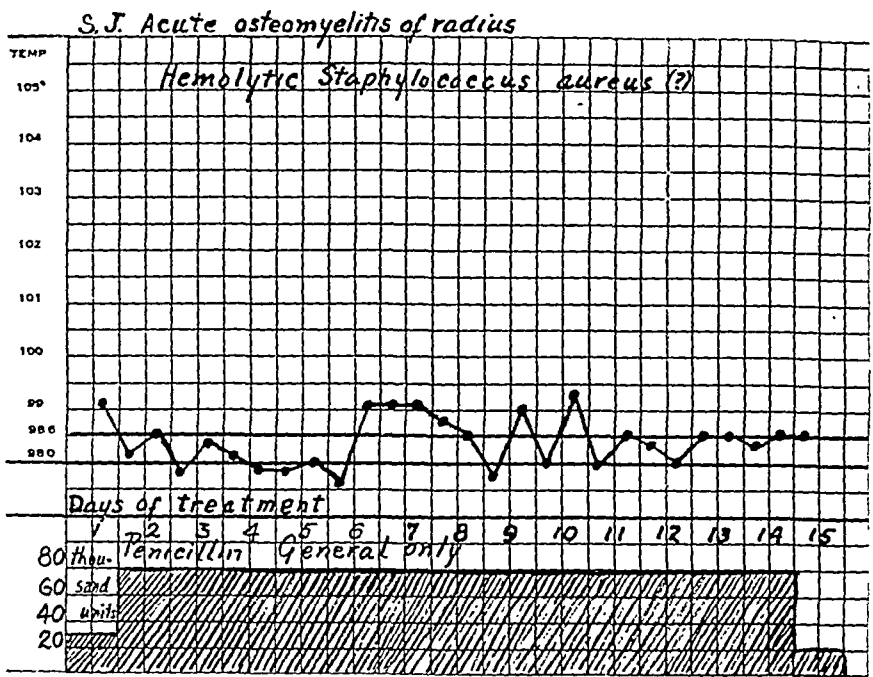
Case IV

Case III: W. C. A boy of 16 had an acute hemolytic *Staphylococcus aureus* diffuse cellulitis of the thigh threatening septicemia and suppurative arthritis of the knee. Failing to respond to sulfadiazine, it resolved promptly following systemic intramuscular administration of 80,000 units of penicillin daily for a week.

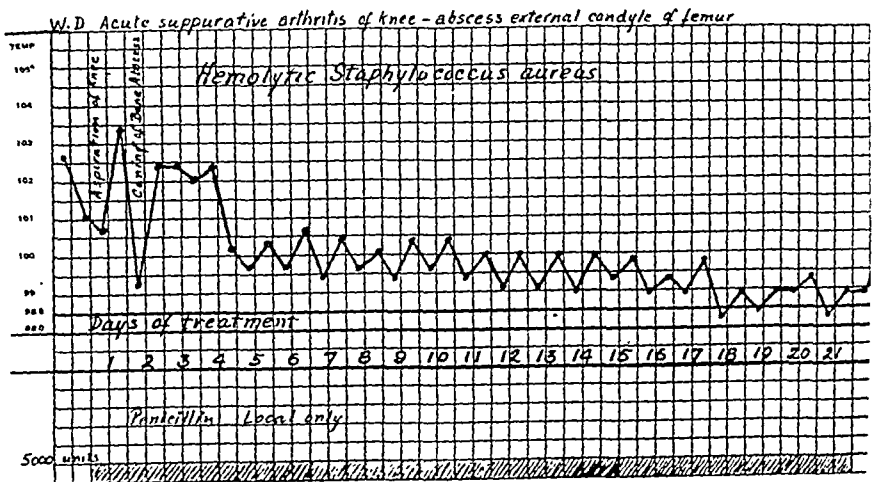
Case IV: C. B. A doctor of 32 had a hemolytic *Staphylococcus aureus* and non-hemolytic streptococcus cellulitis of the cheek and orbit following a Caldwell-Luc operation of the antrum. It failed to respond to the sulfonamides, although the temperature fell initially it sharply rose again. After the second dose of 10,000 units of intramuscular penicillin the patient volunteered the information that he suddenly felt free of the infection. The local process rapidly subsided but X-rays revealed some osteomyelitic changes of the malar bone which may be heard from later.



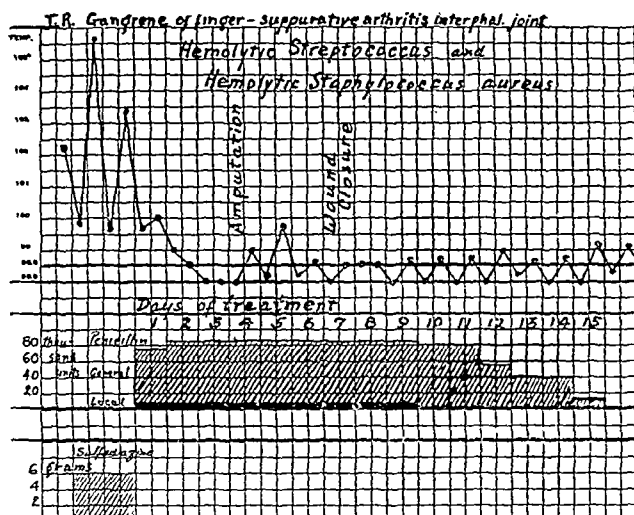
Case V: C. H. A boy of 11 came in suffering from a hemolytic *Staphylococcus aureus* osteomyelitis of the femur and suppurative arthritis of the knee. Before admission he was given relatively small doses of penicillin intramuscularly and locally by needle into the knee joint. The process subsided following repeated aspiration of the knee joint and immobilization in a spica without further operative procedures.



Case VI: S. J. A boy of 18 who had had an old history of recurrent osteomyelitis of the tibia, developed a sudden acute osteomyelitis of the radius. Five of seven attending surgeons judged that it would need surgical drainage. He was given intramuscular penicillin 10,000 units every three hours for fourteen days. The process promptly began to resolve and in three weeks he was able to return to work. X-ray films showed a progressive regeneration of the bone.

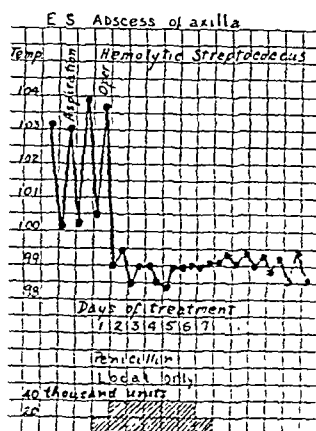


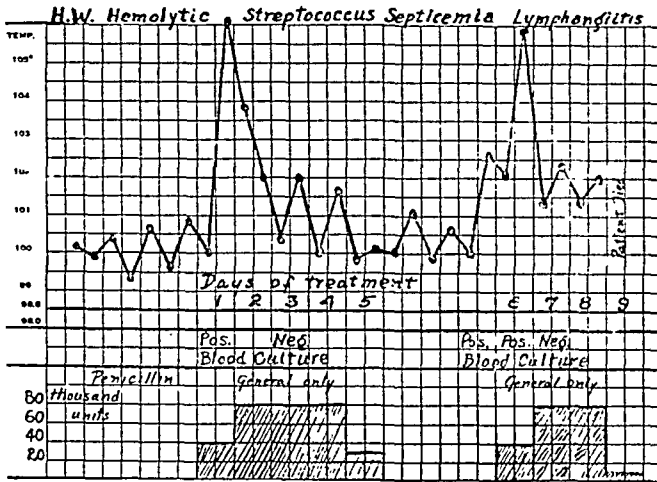
Case VII: W. D. A boy of 14 had had a sequestrum removed from a sinus tract leading down from a suppurative focus in the external condyle of the femur five years previously. He returned with a large bone abscess filling the external condyle and a suppurative arthritis of the knee joint. The knee was aspirated and 5000 units of penicillin were instilled just once. Next day the bone abscess was coned out and packed with gauze soaked in 5000 units of penicillin within a China silk tampon. The penicillin soaked packing was changed daily thereafter and the silk tampon was removed on the seventh day when the bone cavity was found to be lined with granulations. They quickly filled up the cavity and the patient left the hospital on the 27th day. The wound was fully healed in seven weeks. The knee joint returned to perfect function without incision or further aspiration.



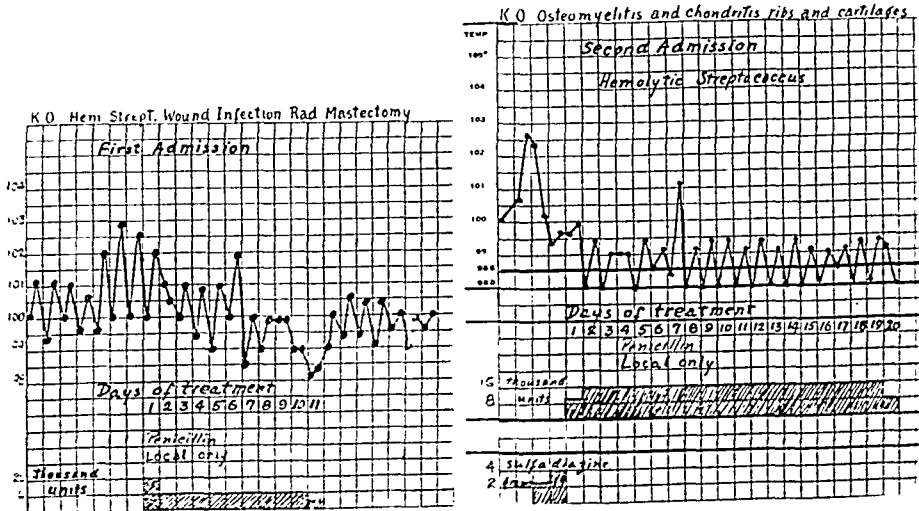
Case VIII: T. R. A Merchant Marine cadet of 20, six weeks before admission had injured his left index finger while cleaning an engine head. It became infected and a slow gangrenous process developed alongside the nail. Two weeks before admission a similar area of gangrene developed over the proximal interphalangeal joint. This slowly ate down to the extensor tendon, dissolved it and consumed the cartilage of the joint. Cellulitis then spread alarmingly up the hand. Both hemolytic streptococcus and hemolytic Staphylococcus aureus were cultured from the wound obviously acting in synergism to produce a gangrenous type of infection. No anaerobes were found. The process was checked by local and intramuscular penicillin. Three days later the finger was amputated at the joint with a long anterior skin flap which was closed on the third day when cultures revealed a disappearance of the streptococcus and marked decrease of the staphylococcus. The wound healed by primary union.

Case IX: E. S. A woman of 62 developed a huge abscess of the axilla following a hemolytic streptococcus infection of the hand: 400 cc of pus were removed by aspiration and 1000 cc more next day through a small incision. Tubes were inserted into the cavity through which 10,000 units of penicillin were introduced every six hours for six days. The fall in temperature was abrupt and convalescence was rapid. Perfect function of the arm resulted.

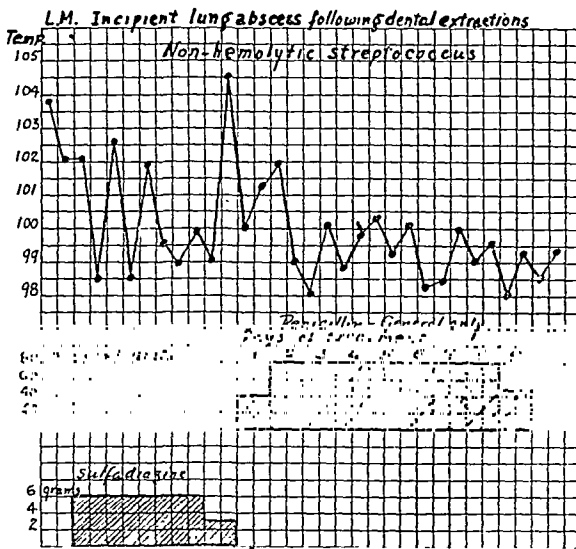




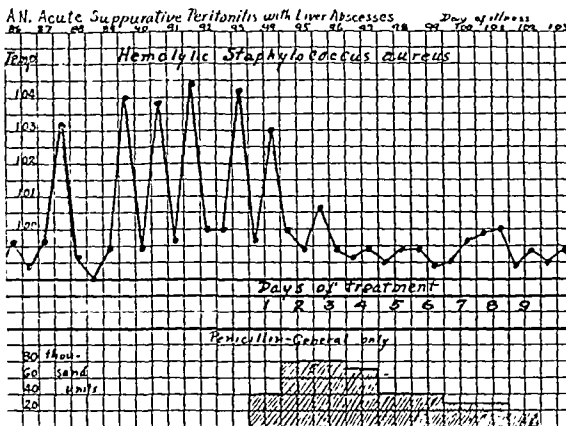
Case X: H. W. A man of 63 with a history of six previous coronary attacks developed a hemolytic streptococcus septicemia following a cellulitis of the thumb. Lymphangitis of the arm followed incision of the thumb and the temperature rose to 106. Temperature fell promptly following the intramuscular administration of 10,000 units of penicillin every three hours and the blood culture became sterile. Penicillin was stopped after four days but three days later the septicemia recurred with another spike of temperature to 105 without obvious reactivity at the portal of entry. Penicillin was resumed and the temperature again fell and blood culture again became sterile. Fluid collected in both chests and was removed by tapping. Cultures yielded no growth. However venous pressure gradually mounted to over 200 and he suddenly died on the fourth day of the second series of penicillin treatments.



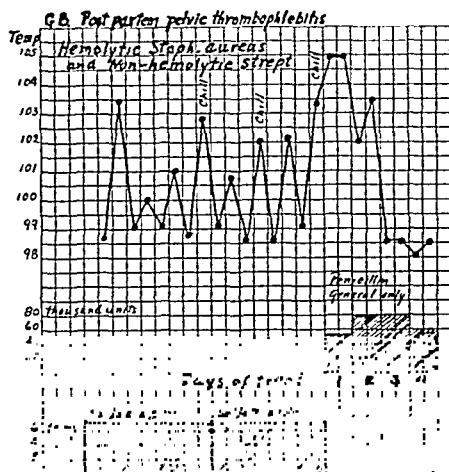
Case XI: K. O. A woman of 52 developed a wound infection yielding hemolytic streptococci following a radical mastectomy. Local penicillin 10,000 units daily was of questionable benefit but the infection slowly cleared up. Within a few weeks however infection recurred in the ribs and cartilages. After surgical removal of the diseased bone and cartilage and continued local treatment with 16,000 units of penicillin daily, the wound finally closed and has remained closed for four months.



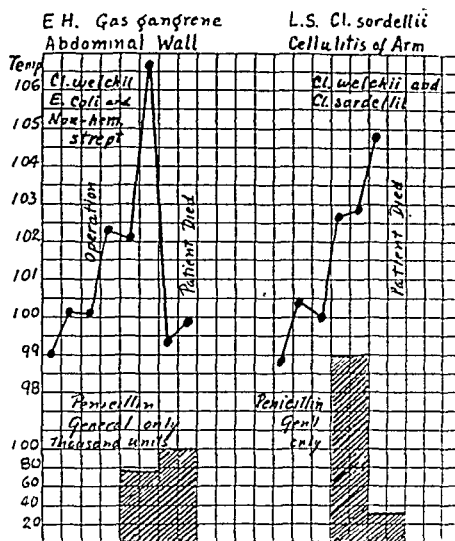
Case XII: L. M. A hospital supervisor of 53 developed signs of pneumonia and incipient lung abscess, six days after the extraction of seven infected teeth. She failed to respond to sulfadiazine and the disease continued to spread in the lungs. Following the intramuscular injection of 10,000 units of penicillin every three hours the process steadily but slowly resolved. She complained bitterly of pain at the site of injection but accepted it for a full course of eight days.



Case XIII: A. N. A man of 64 had been ill with recurrent chills and fever and jaundice for two months. A sudden development of severe upper abdominal pain led to an exploration. Pus was extensively spread around the upper abdomen and masses were found in the liver presumably liver abscesses. The abdomen was closed without drainage. Unfortunately the cultures of the pus yielded no growth. After operation two blood cultures were negative but the fifth postoperative day following a chill, a blood culture yielded hemolytic *Staphylococcus aureus* in one flask. He was given sulfadiazine but he ran an irregular fever for 24 days. Then he began to spike daily up to 103-104 with frequent chills. Intramuscular penicillin was started on the 31st postoperative day and continued with 10,000 units every three hours. Temperature fell dramatically and remained normal thereafter and penicillin was continued for nine days. He left the hospital four days later.



Case XIV



Case XV and XVI

Case XIV: G. B. A woman of 27 developed a postpartum pelvic thrombophlebitis beginning on the third day with daily spikes of temperature and frequent chills. Cultures of the lochia revealed hemolytic *Staphylococcus aureus* and non-hemolytic streptococcus. Temperature fell dramatically on the second day of intramuscular penicillin with 10,000 units every three hours and remained normal. Penicillin was continued for only two more days and her symptoms did not recur. This was probably an unsafe margin but enough in this instance.

Case XV: E. H. A woman of 51 developed a gas gangrene of the abdominal wall following drainage of a common bile duct from which stones were removed and a culture obtained yielding *Cl. welchii*, *E. coli* and non-hemolytic streptococcus. The rectus muscle above the oblique R. U. Q. wound was found liquified and was scraped out. Zinc peroxide was applied locally and both penicillin and polyvalent gas gangrene serum were given intravenously—the penicillin was given in doses of 50,000 units every three hours. During the night, the temperature rose to 106° and then fell in the morning to 99°. She seemed better but jaundice supervened with signs of pulmonary edema and she suddenly died. The benefit of penicillin was questionable. Autopsy showed no evidence of gas in the tissues and the local process seemed to be controlled. She evidently died of the pulmonary and hepatic toxemia.

Case XVI: L. S. A woman of 31 came to the hospital with a rapidly spreading edema of the left arm following a hypodermic injection for asthma. It was at first thought to be an allergic reaction. She repeatedly went into shock only to be restored temporarily by plasma. Incision revealed an edematous fluid which cultured *Cl. sordellii* in large numbers and *Cl. welchii* in decidedly smaller numbers. There was no gas in the tissues nor involvement of the muscle. She was given 50,000 units of penicillin intravenously every three hours but this was obviously ineffective for the edema spread relentlessly. Further incisions likewise failed to halt the spread of the process down the forearm to the hand and over onto the chest wall. Temperature rose steadily to 104° and she died on the 5th day 22 hours after the administration of penicillin during which she received 230,000 units.

study of established infections under the Subcommittee on Infected Wounds and Burns of the National Research Council.

2. A more detailed analysis from a surgical viewpoint of these and other similar cases will have to await the availability of special summary sheets which have been approved by the Subcommittee on Infected Wounds and Burns and by Chairman Lowell Reed of the Subcommittee on Biostatistics of the National Research Council.

3. The differences between medical and surgical infections have been pointed out and the difficulty of evaluating drugs in the treatment of surgical infections has been reiterated.

4. Certain criteria for demonstrating the value of drugs in surgical infections have been proposed.

5. Tables have been presented grouping the cases according to diagnosis, bacteriology, method and dosage and duration of penicillin administration and associated surgical procedures as well as previous and accompanying sulfonamide treatment. The results have been listed as "excellent," "good," "questionable," and "none."

6. Brief clinical abstracts and figures have been presented of illustrative cases with graphs showing the relationship of temperature curves to drug treatment.

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PHYSIOLOGICALLY DIRECTED THERAPY IN THE TREATMENT OF INTRACTABLE BRONCHIAL ASTHMA*

ALVAN L. BARACH

INTRODUCTION

THE purpose of this paper is to present a method of treatment that is derived neither from the allergic nor the simply palliative approach but more especially from an evaluation of the disturbed physiology that results from persistent bronchial spasm. Although a cure of the disease is not the aim of physiologically directed therapy, a more lasting freedom from the symptoms of severe asthma takes place with sufficient frequency as to justify a review of the principles on which it is based. It should be emphasized at the outset that every patient with bronchial asthma should be investigated carefully by a physician with special training in allergy, and that the present program for the relief of intractable asthma is not intended as a substitute for the search for specific etiological factors.

A frequent observation of doctors who see patients with bronchial asthma is that a remission in the disease at times takes place in which the patient is for a variable period free from the distressing symptoms of more or less continuous asthma. This abrupt cessation of bronchial spasm has been seen after an acute illness with high fever, such as pneumonia. The intention of physiologically directed therapy is to initiate a somewhat similar remission and to provide the means of maintaining it for a relatively prolonged period. The principle of treatment consists of repeated bronchial relaxation by the cumulative effect of various measures which act in this direction. Although remissions in intractable asthma were first obtained by the author as a result of intermittent inhalations of helium-oxygen mixtures, repeated bronchial relaxation may now be secured in many cases without the use of helium therapy.^{1,2,3,4} In cases in which the provision of effective helium therapy

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Friday Afternoon Lecture March 17, 1944 at The New York Academy of Medicine.

is not feasible, the continuous administration of oxygen is indicated if anoxia is present, to overcome the effects of oxygen want on the cardio-respiratory and central nervous systems. The disadvantage of prescribing helium is the technical difficulty of administering it efficiently, as well as the expense of the gas itself and frequently an incomplete understanding of the purpose for which it is intended. For these reasons other measures, including the effective use of aminophyllin, may well be tried first.

PATHOLOGICAL PHYSIOLOGY OF OBSTRUCTIVE DYSPNEA

The consequences of experimental tracheal constriction in dogs will be briefly reviewed since the effects produced in this way may aid our understanding of obstructive dyspnea in man. When a dog is required to breathe through a constricted orifice, such as one-eighth of an inch, the increased physical effort made necessary is immediately portrayed by a marked rise in negative intrapleural pressure during the inspiration and by a pressure during expiration which approaches that of the atmosphere. Prolonged obstructive dyspnea results in congestion and edema of the lungs, more marked at the bases, with areas of emphysema at the periphery. If an animal is subjected to tracheal constriction only during the *inspiratory* cycle, with expiration free, these changes are still present, since the elevated negative pressure within the chest results in a suction action on the alveoli and on the intrathoracic bronchi, with the production of edema in the alveoli and swelling of the bronchial mucous membranes.^{5,6,7} In addition, there is a readier inflow of blood into the lungs and an increased difficulty in the exit of blood from the lungs into the left heart and from the left heart into the aorta. The pulse becomes more rapid, the volume disappears during the inspiratory cycle and the dog finally dies of asphyxia, due to extensive damage in the lungs and cardiac failure.

When inspiration is allowed to be free and tracheal constriction is created during expiration, the changes just described do not take place and the animal at the end of six hours appears to be in good condition. The conclusion to be drawn from separating the effects of obstruction during inspiration from those during expiration is that the heightened negative pressure within the lung during the inspiratory cycle is the critical pathogenetic factor responsible for damage to the lungs.

When obstructive dyspnea is due to constriction in the larynx or

in the trachea outside the chest, inspiration and expiration are equally prolonged. The increase in the volume of breathing is at first stimulated by proprioceptive reflexes from the lungs. Later, as pulmonary congestion and edema take place, as well as swelling of the mucous membrane of the bronchi, dyspnea is aggravated by anoxia and accumulation of carbon dioxide. The increased ventilation may in the beginning result in a blowing off of carbon dioxide, with a transient and slight shift in pH toward the alkaline side but as pathological changes take place in the lungs the efficiency of CO_2 elimination is impaired and carbon dioxide retention results, accompanied by a lowering of the arterial oxygen saturation. When obstruction takes place in the bronchial passageway within the chest, expiration is prolonged since the intrathoracic bronchi constrict during expiration, as the volume of the chest is diminished. Since constriction of the bronchioles is enhanced during expiration, the outlet of air from the alveoli is hindered; the alveolar cells are additionally distended by the succeeding inspiration which puts increased pressure on the pulmonary capillaries and at times results in rupture of their walls. In patients with bronchial asthma an increase in pulmonary ventilation, brought on either by exercise or bronchial spasm, may result in a temporary over-distention of the lung alveoli. This functional pulmonary emphysema may disappear when a remission takes place. In some patients, especially in those in whom infection in the bronchi is present, repeated and prolonged bronchial spasm may result in varying degrees of permanent pulmonary emphysema.

The inhalation of helium with oxygen was shown to result in a lowered negative intrapleural pressure during inspiration in dogs in whom tracheal obstruction had been produced.⁸ In one patient with severe asthma the inhalation of an 80 per cent helium 20 per cent oxygen mixture was shown to result also in a substantial decrease in the pathologically elevated negative intrapleural pressure during inspiration.¹

The substitution of helium for nitrogen is of value in obstructive dyspnea since the velocity of movement of a gas through a constricted orifice is inversely proportional to the square root of the density of the gas. This formula, known as effusion, is the same as the law for diffusion of gases. Since a helium-oxygen mixture is one-third the weight of air or oxygen, the pressure required for the movement of an 80 per cent helium 20 per cent oxygen mixture past a point of localized obstruction was considered to be almost one-half that required for pure

oxygen. Thus, when an oxygen regulator was placed on a helium-oxygen cylinder and set at a liter flow of 1.0, it was observed that the volume of gas passing into a spirometer was 1.7 times the volume of gas that came from a cylinder of oxygen. If the constriction was prolonged in a linear direction, the factor of viscosity would then become involved and, since helium has in fact a slightly higher viscosity than nitrogen, no increase in flow would be observed. In patients with asthma the obstruction is generally in the smaller bronchioles and is fortunately not continued to a sufficiently linear degree as to prevent relief from breathing the helium-oxygen mixture. In some patients, the flow of air is probably modified by both the factors of effusion and viscosity. In localized obstruction in the larynx and trachea the pressure required to breathe helium with oxygen is markedly less than that necessary for ventilating the lungs with oxygen or air.

Dean and Visscher⁹ have emphasized turbulence in gas movement, in explaining the relief of dyspnea accomplished by helium-oxygen inhalation in experimental tracheal obstruction; analysis of their formulae reveals that the velocity of turbulent flow is also approximately inversely proportional to the square root of the density of the gas used. We have repeatedly pointed out that there is no change in the effort of respiration during quiet breathing when helium is substituted for nitrogen; its use was proposed for the treatment of *obstructive* dyspnea and its effectiveness in this respect has been confirmed by others.^{10,11,12,13}

The effect of inhaling 25 per cent oxygen with 75 per cent helium is, therefore, to diminish the physical pressure required to ventilate the lungs in conditions of laryngeal and tracheal obstruction and severe asthma. This decrease in physical effort (and in the negative intrapleural pressure during inspiration) may be accompanied by a progressive relaxation of the constricted bronchial muscle when the procedure is carried out for one to two hours twice a day for a period of five days.

Positive pressure respiration was added to helium-oxygen administration to increase the relief obtained by inhalational therapy of obstructive dyspnea, and to combat edema of the lungs.⁶ The physiological basis of this procedure was described as follows: (1) The specific importance of inhaling a gas under increased pressure is to decrease the pathologically elevated negative intrapulmonary pressure which is present during the inspiratory cycle in cases of obstructive dyspnea. (2) Breathing under a pressure of 10 to 13 cm. of water enormously facili-

tated the entrance of a therapeutic gas during inspiration. (3) During expiration the lumen of the smaller bronchioles was less constricted. (4) The increased intrapulmonary pressure decreased the accumulation of blood in the lungs by exercising a retarding effect on the entrance of blood into the right heart. (5) In animal experiments edema of the lungs was produced when an atmosphere was inhaled under a negative pressure of 6 cm. of water for 6 hours. (6) The inhalation of a gas under positive pressure decreased the suction action of negative pressure on the pulmonary capillaries and in that way tended to clear pulmonary edema.

Poulton,¹⁴ utilizing the suggestion and the apparatus of Plesch,¹⁵ reported that positive pressure breathing afforded "some relief in seven cases of paroxysmal dyspnea" and that "out of eleven cases of asthma good results were obtained in three cases." However, pressure was given in these clinical trials for brief periods only. The relief of paroxysmal dyspnea could be ascribed to a lessened entrance of blood into the right heart and therefore in the lungs, which enabled the left ventricle to deal more effectively with a smaller volume of blood. It had been shown by Weiss and Robb¹⁶ that attacks of cardiac asthma were associated with a sudden increase in the volume of blood in the lungs. The physiological events which took place during the inhalation of oxygen under positive pressure were studied in human subjects and the favorable results that followed the use of continuous positive pressure respiration in some cases of acute pulmonary edema have been described, as well as the apparatus and technique of administering pressure breathing.^{17, 18, 19, 20}

TREATMENT OF INTRACTABLE ASTHMA

In the treatment of status asthmaticus an oxygen-enriched atmosphere is provided to prevent respiratory or cardiac failure during the period in which bronchial relaxation is attempted. The inhalation of 50 per cent oxygen in a tent or by means of a catheter inserted in the nasopharynx or oropharynx is better than a mask for oxygen therapy, since most patients with asthma cannot tolerate continuous application of a close-fitting mask to the face. If helium-oxygen therapy is available, inhalation of 25 per cent oxygen with the remainder helium for two hours twice a day, preferably in a positive pressure hood, is employed; the patient is replaced in a tent or given oxygen by catheter

after the helium inhalation. If the hood is not available, the helium-oxygen mixture may be inhaled by a mask but precautions should be taken to maintain a sufficiently adequate flow of the helium-oxygen mixture to prevent negative pressure developing within the mask. If the meter mask is used, the inspiratory valve is either removed, or a match is inserted underneath it so that it is continuously open. A flow of 6 to 9 liters of the helium-oxygen mixture is given for periods of three-quarters of an hour and repeated two or three times during the day.

In the treatment of intractable asthma, in the absence of a grave state of the patient known as status asthmaticus, a similar program of inhalational therapy may be used. In the absence of anoxia the continuous employment of oxygen-enriched atmospheres is not necessary. Since the introduction of intravenous aminophyllin the necessity for keeping patients with status asthmaticus *continuously* in a helium-oxygen atmosphere under positive pressure is no longer present. In a few instances, however, this technique of treatment may be required.

When inhalations of helium-oxygen mixtures are used to produce local bronchial relaxation, the indication is *not* to relieve paroxysms of severe asthma; these may be too severe to be relieved by inhaling helium with oxygen. During the state of slight, moderate, or marked wheezing respiration characteristic of many patients with intractable asthma, the inhalation of helium-oxygen mixtures is of special usefulness. In most patients who are treated efficiently both subjective and objective relief will be apparent as the result of inhaling a mixture of 20 to 25 per cent oxygen and 75 to 80 per cent helium. This relief is more marked when positive pressure hoods are used but is also apparent in mask treatment. The effect of one inhalation is generally to provide only temporary alleviation of symptoms but repeated inhalations of this gas mixture over a period of five days appear to result in a cumulative effect and, therefore, may be used as part of a program of repeated bronchial relaxation. In addition to the local relaxation of the bronchi which this lighter-than-air gas mixture may promote, the negative intrapulmonary pressure during the inspiratory cycle is decreased, so that the mucous membrane of the bronchioles is exposed to a decreased suction effect. In addition, there is better ventilation of the alveoli through constricted orifices.

In recent years we have employed *repeated* injections of aminophyllin in a manner similar to the use of repeated inhalations of helium

with oxygen, at times without inhalational therapy and at other times in conjunction with it. The introduction of intravenous administration of aminophyllin constitutes a landmark in the treatment of intractable asthma.^{21, 22} It must be pointed out at the outset, however, that one or two injections of this drug may not result in a satisfactory remission in the symptoms of severe bronchial asthma. In many cases intravenous injection of aminophyllin twice a day for a period of a week and once a day for a period of several weeks to several months might be necessary to break a state of persisting bronchial spasm. Since this would represent an extensive use of intravenous medication, it was fortunately discovered that aminophyllin may be given rectally in watery solution with a beneficial effect almost as great as that obtained from the intravenous route and with the advantages of the absence of circulatory reactions and the obvious usefulness of a method that can be employed by the patient at home.²³

The technique of administration is important; aminophyllin powders of 0.5, 0.6 or 0.7 Gm. are dissolved in 20 cc. of tap water and instilled into the rectum by a rubber catheter attached to a 20 cc. glass syringe. If a well lubricated No. 10 French catheter is employed the rectal method of injecting aminophyllin is capable of being used by the patient without irritation night and morning for the first week, and for a period of several weeks or several months thereafter, if necessary. Aminophyllin by mouth and by suppository may be helpful in controlling mild or moderate asthma but absorption is too slow to accomplish bronchial relaxation in instances of severe bronchial spasm. Repeated intramuscular injections are impractical because they produce considerable soreness in the gluteal region. The method of rectal instillation is convenient since the patient may have a number of powders made up and quickly provide for himself this type of treatment, with relief of severe asthma, without making it necessary to call a physician to administer an intravenous dose of the drug. In cases that respond favorably to rectal instillation of aminophyllin and the other procedures to be described, a decrease in the severity and incidence of attacks of asthma sets in within a period of five days. A remission may be produced in some cases which lasts from several months to, at times, several years.

The administration of potassium iodide in a dose of 1 cc. of the saturated solution morning and night is considered helpful, not only to

produce a free flow of mucus and to prevent crusting but also because iodides appear to decrease the tendency to asthma. It must be borne in mind that excessive use of iodides may cause a bronchorrhea and thus result in the production of more mucus than the patient will be able to expectorate. In these cases iodides should be stopped for a period of time or given in small doses such as 0.3 or 0.5 cc. daily.

Although morphine may produce respiratory depression if given in excessive dosages, this drug is of great value in many cases, especially when the morphine substitute, dilaudid, is employed. The administration of dilaudid is generally given by mouth, $1/20$ gr. to adults, although smaller doses by hypodermic, gr. $1/32$ to $1/64$, may be given for the first 2 to 5 days. Since this drug may result in addiction, it should be stopped at the end of five days. No instance of respiratory failure or other harmful effect of dilaudid has been observed in over 100 patients in whom it has been used repeatedly during the first 5 days of treatment. The effect of both central nervous system relaxation and bronchial relaxation may be observed in the majority of patients with intractable asthma following its judicious administration. Recently, we have employed demerol in order to accomplish a similar result without the potential hazard of addiction; it is evident that this drug is also of unquestionable value in reducing psychic tension and in promoting bronchial relaxation, given either by mouth or by injection in 100 mg. doses. The injection of sodium luminal is apt to result in better sedation than administration of barbiturate drugs, such as sodium amytal, seconal or nembutal, which sometimes result in irrationality and excitability. A dosage of 0.1 to 0.2 Gm. may be given by hypodermic once or twice a day.

Another procedure that may be of marked value in the program of bronchial relaxation is the inhalation of 1 per cent neosynephrin, carried out by passing oxygen from a high pressure cylinder at a flow of 5 liters per minute through a nebulizer.²³ At two to three hour intervals, 0.5 cc. of 1 per cent neosynephrin is inserted in the nebulizer, and the wide end held within the mouth so that the patient continuously inhales the nebulin of neosynephrin produced by the stream of oxygen. Although this drug is not a good bronchodilator, it exercises a vasoconstricting effect on the mucous membrane and often produces a more patent respiratory passageway, with considerable increase in the vital capacity. The patient with asthma or pulmonary emphysema does not

appear to become refractory to this drug. This procedure of intermittent inhalation of neosynephrin is generally continued for five days. If bronchial infection is present, it may be followed by nebulization of sulfadiazine in 2½ per cent ethanolamine (Pickrell) solution, in dosages of 1.5 cc., repeated in two to three hours.

Epinephrine, 1 to 100, may also be given by this continuous method of nebulization in dosages of 0.2 to 0.5 cc. The hand bulb method of nebulizing epinephrine²⁴ will generally be effective in relieving asthma after the patient has obtained a degree of bronchial relaxation. During the first 5 days of treatment, epinephrine may be given either by injection or by nebulization to modify the severity of bronchial spasm but since patients with intractable asthma characteristically become refractory to epinephrine in all forms, it is better to postpone use of this drug until the aim of treatment has been accomplished. Repeated injection of adrenalin does not result in cumulative bronchial relaxation, which appears to set in more promptly when epinephrine is dispensed with. Following a favorable outcome of the program described, inhalation of the nebulin of 1 to 100 epinephrine is more satisfactory than hypodermic administration in abolishing attacks of mild or moderate asthma.

In patients with severe inspiratory dyspnea, oxygen-enriched atmospheres, or helium-oxygen mixtures, may be given under continuous positive pressure in a hood designed for this purpose as well as for the treatment of pulmonary edema.¹⁸ The principles and techniques of various types of inhalational therapy have been recently described.²⁵

In patients in whom considerable asthma persists after a week of administration of aminophyllin, iodides, dilaudid or demerol, neosynephrin, sodium luminal, either with or without oxygen or helium-oxygen therapy, additional measures should be tried. The rectal injection of ether in doses of 60 to 90 cc. mixed with equal parts of olive oil is at times followed by bronchial relaxation.²⁶ This may be repeated two or three times at intervals of two days if necessary. In some cases of persisting bronchial spasm, the use of typhoid vaccine to create a slight fever may be helpful. This may be given by intramuscular injection, 1 cc. of the triple typhoid vaccine. A higher fever is more effective and may be produced with a small dose of vaccine when given intravenously. The intravenous injection of typhoid vaccine is more safely administered if 0.2 cc. of the vaccine is added to 1,000 cc. of

normal saline and a slow drip infusion is carried out.²⁷ When the patient develops a chill the administration of the vaccine in saline may be stopped. If a temperature of 102 to 104°F. has been produced, the severity of the symptoms of asthma may be notably lessened thereafter. However, more than one injection of typhoid vaccine may be required to terminate a state of intractable asthma in some patients.

Although repeated bronchial relaxation is followed by a remission in the symptoms of the disease in the majority of patients with intractable asthma, there are still a good many in whom the relief obtained is unfortunately either temporary or slight. In these patients, continued use of aminophyllin may be necessary either by mouth in dosages of 0.2 Gm. two or three times daily, or rectally, 0.6 Gm. once or twice a day for a long period. In most patients the administration of epinephrine by means of a nebulizer has been found to be more satisfactory than by hypodermic injection for palliative relief. If an *adequate* dosage of aminophyllin is taken, attacks of moderate asthma can generally be controlled by inhaling the nebulin of a 1 per cent epinephrine solution. The inhalation of a nebulized solution is more practical for patients than hypodermic injection and the small dosage results in less systemic effect than parenteral administration.

SUMMARY

Studies of the pathological physiology of obstructive dyspnea indicate that the elevated negative intrapulmonary pressure during the inspiratory cycle exercises a harmful influence on respiratory function. Lowering of this negative pressure by appropriate inhalational and drug therapy is of value in preventing pathological changes in the lungs and intrathoracic bronchi.

Physiologically directed therapy in status asthmaticus may include the inhalation of helium-oxygen mixtures to provide a less effortful type of breathing, or oxygen-enriched air to prevent the effects of anoxia on the cardiac and respiratory systems.

In many patients with intractable bronchial asthma, a program of repeated bronchial relaxation may be pursued without necessarily employing inhalational therapy. The principle of treatment consists of the use of measures which promote relaxation of the constricted bronchial muscle. These include administration of aminophyllin by intravenous or, more conveniently, by rectal instillation of an aqueous

solution, potassium iodide, dilaudid or demerol, neosynephrin by nebulization, and sedation, preferably with sodium luminal. Intermittent inhalation of helium-oxygen mixtures may be added to this regimen since it is helpful during the first 5 days in promoting local bronchial relaxation.

In cases in which the program of bronchial relaxation results in only temporary alleviation of symptoms, a continuation of some of the procedures used is indicated. Administration of aminophyllin in adequate dosages by mouth or by rectal instillation may be required for a prolonged period to prevent recurrence of severe asthma. In these cases, other measures may be tried, such as anesthetic doses of colonic ether and the production of fever with typhoid vaccine.

In the majority of cases of intractable asthma, a more satisfactory remission of the symptoms of the disease may be obtained by the concentrated employment of procedures which produce in one way or another cumulative relaxation of constricted bronchial muscles than by simple palliative therapy.

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1944

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MAY 25, 1880—AUGUST 30, 1944

DAVENPORT, CHARLES BENEDICT

JUNE 1, 1866—FEBRUARY 18, 1944

DILLINGHAM, FREDERIC HENRY

APRIL 7, 1857—AUGUST 30, 1944

GILFILLAN, WILLIAM WHITEHEAD

DECEMBER 14, 1868—FEBRUARY
10, 1944

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DECEMBER 6, 1869—APRIL 22, 1944

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FEBRUARY 28, 1872—FEBRUARY 27,
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GWATHMEY, JAMES TAYLOE

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11, 1944

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NOVEMBER 4, 1868—AUGUST 27,
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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



NOVEMBER 1944

THE PRACTICAL MANAGEMENT OF
HYPERTENSION *

MILTON BENJAMIN ROSENBLÜTH

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WHEN a physician is called upon to take care of a patient with hypertension his first problem is to try to account for the hypertension on the basis of one of the known causes of hypertension. There are many such conditions but, for the most part, they are uncommon or rare. Nevertheless the possibility of one of these conditions being present must be kept in mind and they must be carefully ruled out before one may classify a case as one of essential hypertension or, in other words, as being of unknown etiology. The most important of these conditions to be looked for are glomerulonephritis, pyelonephritis, polycystic kidneys, hydronephrosis, congenital anomalies of the kidney and tumors of the adrenal glands.

UNILATERAL RENAL DISEASE

Especially important to rule out is the presence of a unilateral renal lesion. The interest which has been shown of late in this group of unilateral renal lesions as a possible basis for hypertension and the pos-

* A Friday Afternoon Lecture, April 7, 1944 at The New York Academy of Medicine.

sibility of cure by nephrectomy stems from the observation of Goldblatt that hypertension can be produced in animals by clamping the main artery of one kidney while leaving the other kidney intact and that removal of the treated kidney leads to a prompt fall in the blood pressure, provided the hypertension has not persisted too long.

It should be emphasized that all unilateral renal diseases do not lead to hypertension and that most of those renal conditions which do lead to hypertension are bilateral rather than unilateral. Furthermore, in those cases in which the renal lesion is unilateral, there is no way of knowing for certain which kidney is responsible for the hypertension. Cases in which the possibility of a unilateral renal lesion as the cause of the hypertension is suspected should be studied by all the indicated methods such as intravenous urography, and if necessary retrograde pyelography, cystoscopy and urine cultures. Two difficulties that stand in the way of this method are that we have no way of identifying with certainty the offending kidney and that removal of any normal tissue from a hypertensive patient may aggravate rather than improve the hypertension.

The chance for successful treatment by unilateral nephrectomy is greatest in young people and in those in whom the hypertension has not existed long enough to produce secondary changes in the heart, peripheral vessels and the other kidney.

At the Mayo Clinic, Braasch, Walters and Hammer studied 1,684 patients who were subjected to renal surgical procedures. They found that the renal lesion amenable to surgical treatment which occurs most often in association with hypertension is atrophic pyelonephritis. Hypertension occurred in 20 of 43 patients operated upon for primary atrophic pyelonephritis, or 46.5 per cent. Hypertension was observed in 20.3 per cent of 793 cases in which operation was performed for renal stone and in 14 per cent of 372 cases of hydronephrosis without stone. Hypertension was observed less frequently in the presence of renal tuberculosis than in most other forms of surgical kidney. It was present in 7.6 per cent of the 158 cases studied. Hypertension was found in 27.7 per cent of 137 cases in which operation was performed for renal adenocarcinoma.

It was found that the hypertension was relieved in approximately 70 per cent of cases of atrophic pyelonephritis, in 50 per cent of cases with renal tuberculosis and in 25 per cent of cases associated with renal

calculus, hydronephrosis or tumor.

Although the hypertension associated with surgical lesions of the kidneys is relieved more often by nephrectomy than by conservative operations, the blood pressure often returns to normal after nephrolithotomy and renal drainage. Hypertension alone is not sufficient reason for sacrificing a kidney with a calculus which is easily removable, or a hydronephrosis which might be corrected by a plastic operation, or a cortical infection which is amenable to chemotherapy and drainage. A good rule of thumb is that in patients with hypertension and unilateral renal lesions nephrectomy is indicated only if that would be the procedure of choice without reference to the hypertension.

COURSE AND PROGNOSIS

After having made certain that the patient whom you are studying has none of the conditions known to cause hypertension you may label him as having essential hypertension and this diagnosis will be applicable in about 95 per cent of hypertensions. It will be found very helpful when beginning to take care of such a case to have clearly in mind what usually happens to such cases and then to determine what is likely to happen to the particular case you are dealing with. You should take stock of the patient, appraise the physical status, estimate how much damage has already been done and then try to evaluate the further course.

It appears certain that essential hypertension is an hereditary disease and that hypertensives are born with the hypertensive trait. Many years may pass before hypertension appears but even during this prehypertensive period the tendency can be shown by a positive response to the cold pressor test. The next phase in the evolution of the disease is the period of intermittent hypertension when the elevated pressure may be present under stress or excitement, only to return spontaneously to a relatively normal pressure. Finally there is the phase of permanent hypertension. Obviously the clinical picture and the prognosis too will vary considerably depending upon which phase in the natural evolution of the disease the patient is in when seen.

Some of these patients who are picked up as a chance finding are completely free of symptoms, and may run a course of twenty to thirty years and die of some wholly unrelated condition. Others run a malignant course with very distressing symptoms and die within a

year or two of the onset. And in between these two extremes are the vast majority of hypertensives who run their course in about ten to fifteen years and who die of one of the effects of hypertension. On first seeing a patient we cannot know into which of these groups he should be placed. It is only after months of observation that we may get some idea of the outlook by observing the rate of progression of the disease, the changes occurring in the various organs and the response to therapy.

Before proceeding further let us see what ultimately happens to these patients. There are good statistical studies which show the cause of death in large series of these cases. The study of Bell and Clawson on 420 patients is fairly representative. They found the cause of death to be myocardial insufficiency in 45 per cent, coronary disease in 15 per cent, cerebral hemorrhage and thrombosis in 19 per cent, renal insufficiency in 9 per cent and accident or intercurrent disease in 12 per cent. So that taking together the cases of congestive failure and the cases of coronary disease the heart was the cause of death in 60 per cent of all cases. (Here, then, is one place where the physician can render genuine help with medical treatment.)

The data which we need in order to evaluate the prognosis in a patient may be grouped under the following headings:

1. *The level of the arterial pressure and its lability.* In general the prognosis is worse the higher the pressure, the height of the diastolic pressure being even more significant than the height of the systolic pressure. It is surprising though to find how often high levels of pressure such as 200—225 systolic, and 110—120 diastolic, are borne without symptoms for years. Nevertheless, one should regard any patient whose systolic pressure is over 250 and whose diastolic pressure is over 150 as definitely in danger.

Quite aside from the height of the pressure, if it remains at a fixed level, the prognosis is generally thought to be worse than when it fluctuates from day to day or hour to hour, or as influenced by sedatives, etc.

2. *The cardiovascular status:* A careful history will often reveal some evidence of *diminished cardiac reserve*, such as dyspnea on exertion or swelling of the feet at night. These symptoms may be very slight, give no serious discomfort and unless specifically enquired for may not be related by the patient.

Hypertrophy of the left ventricle should be looked for by physical examination and x-ray. During the early stages when the hypertrophy is of the concentric type and before dilatation occurs it may be difficult to detect, but even then it may be suspected on the x-ray by the shape of the cardiac silhouette with its accentuation of the cardiovascular angle and a rounding and elevation of the cardiac apex. The electrocardiogram, too, may provide evidence of left ventricular hypertrophy, when there is left deviation of the electrical axis, especially if the patient is a young adult.

Changes in the coronary arteries are suggested by anginal pain and by electrocardiographic changes.

Atherosclerosis of the aorta should be looked for. It presents a characteristic picture on x-ray with elongation, tortuosity, increased density and calcification.

3. *The renal status* should be carefully studied. The renal function is usually unimpaired until relatively late in the disease when the arteriolar sclerosis has led to extensive atrophy of the renal parenchyma. The concentrating power which is a measure of renal tubular function should be determined by any of the well established specific gravity tests. This is more sensitive than the clearance tests to slight degrees of renal damage, and therefore, if the concentration test is normal, one need not measure the clearance. But if the specific gravity is low, a clearance must be done to find out whether it is in the range of 30-40 per cent, which might be consistent with a subjectively well and active condition for several years; or whether the clearance is below 10 per cent with uremia due in a short time. When the clearance falls to 5 per cent of normal the clinical condition of uremia is either present or imminent.

In malignant nephrosclerosis the necrotic lesions in the renal arterioles cause rapid destruction of the kidney parenchyma with decreased function and uremia. In the absence of these necrotic lesions and in otherwise uncomplicated cases only a very small percentage go on to renal insufficiency.

Having determined the state of the heart, blood vessels and kidneys there is one additional fact which we should like to have in judging the outlook in any patient. That is the *duration of the hypertension* up to the time when the patient is first seen. Since the disease runs a long course in the average case, it is obvious that the earlier in the course

he is seen the longer he is likely to last, and the converse is also true. In the occasional patient who has been examined at regular intervals the approximate date of onset of the hypertension may be known; but in most cases, where the presence of hypertension is discovered by chance, it is only by indirect evidence that we may know something about how long it has been present. Such evidence is supplied by the data which I suggested that you collect about the level of the blood pressure and its lability, left ventricular hypertrophy, the anginal syndrome and coronary artery changes as evidenced by electrocardiogram, and atherosclerosis of the aorta as shown by x-ray. If all these data suggest that the hypertension is recent the outlook may confidently be predicted to be good, with the reservation always that an occasional hypertensive, especially those in the age group below 50, may quite suddenly develop malignant hypertension and the entire course be accelerated.

GENERAL TREATMENT

It should be emphasized at the outset that correcting the hypertension, even if that were possible, would not constitute cure of the disease. The hypertension is but one manifestation, though a very important one, of some underlying disease process. The nature and the cause of this process still elude us. Discovering the cause of the hypertension and removing that cause would be the way to help these patients. That ideal therapy is not yet here and until it is we must temporize with methods that leave much to be desired but which, nevertheless, can accomplish something in most cases and much in a few.

In that group of patients to which I referred before, who are fortunate enough to be free of symptoms and whose arterial tension is not very high, no active treatment is indicated. In general I should say that in these patients, especially if they are over 50, one need not attempt the more active methods of reducing the tension, and one should be content to institute a routine of somewhat lessened activity and more rest. Such a regimen should include rest periods each day, after luncheon or before dinner, ten hours of bed rest at night, warm baths for relaxation, a somewhat curtailed business day and vacations as often as the economic situation permits. Alcohol, coffee, tobacco may be used in moderation except by those who are specifically sensitive to

them. The diet need be altered only if the patient is obese, in which case a low calorie diet resulting in loss of weight may also result in a significant reduction in the level of arterial pressure. If the patient is apprehensive, and he is very likely to be, he will need reassurance and much explanation about the probable benign nature of his particular kind of hypertension. It seems wiser never to tell the patient the exact level of his tension or else he will be happy one day when it has gone down some insignificant degree and gloomy and depressed if it has gone up a comparable degree. Not telling the patient is better than deceiving him about the level, for sooner or later he is likely to find you out and his confidence in your integrity will be gone. These patients should not be seen too frequently lest they develop a feeling of invalidism, but they should be seen often enough so that the condition of the heart, vessels, kidneys and eye grounds may be checked. About four times a year would seem to be sufficient for that purpose.

The problem of what to do becomes more difficult in dealing with the group of patients whose tensions are higher and who are suffering from symptoms arising from the disease. To lower the tension, as I said before, is in no sense a cure of the disease; nevertheless, all the pathological changes which occur in this disease can be explained as resulting from the mechanical effects of a persistently elevated arterial tension. Therefore, even though the hypertension is not the primary cause of the disease but only a symptom, it is a symptom which dominates the entire clinical picture and which in its own right can cause all the disabilities which are known to occur in it. Above all, it is the hypertension which is responsible for the cardiac failure and for the arterial lesions which lead to the terminal event in over 75 per cent of all cases. It would seem therefore to be of the greatest advantage to the patient if the arterial tension were lowered.

For the purpose of reducing the tension innumerable remedies have been suggested. Up to the present time no really satisfactory method is available. But if we bear in mind the limitation of each method and the indications of each we can accomplish a great deal for a few selected patients. The routine which I suggest is this: When a patient who has been free of symptoms begins to develop headache, vertigo, irritability, insomnia (which symptoms are referable to the nervous system) or excessive fatigue, dyspnea, precordial pain (which symptoms are referable to the cardiovascular system) he should be given the benefit of

complete bed rest for a period of two to four weeks. The rest should be made as complete as possible and so far as possible he should be spared the usual anxieties and cares that are the lot of most of us. If headache is troublesome the head of the bed should be elevated 12-18 inches.

During this period, if the patient is obese, one may try the effect of weight reduction by a low calorie diet.

This enforced rest in a patient who is ordinarily vigorous and active may occasion restlessness and irritability and it is therefore advisable to use sedatives freely. Phenobarbital or chloral hydrate are the best. Bromide, which tends to be cumulative, is much less innocuous than generally believed.

The patient should be made to understand that the rest cure is of value whether or not the tension is lowered. And the doctor, too, should realize that benefit accrues to these patients by the protective action of rest on the cardiovascular system and the sedative effect on the nervous system, even if there is only an insignificant drop in the tension. In most patients, even though the drop in the tension is considerable, a resumption of their usual activities brings with it the return of the original level of tension.

Among the many drugs that have been suggested for lowering the tension, the only one that deserves serious consideration is *potassium thiocyanate*. This drug was introduced by Pauli in 1903 but the large doses recommended caused such disagreeable symptoms that the drug soon fell into disuse. Its use was revived by Westphal in 1924 and since then each year has witnessed reports on its use, most of which suggest that the drug may prove helpful. And yet the drug has never attained the acceptance which one would expect in the treatment of a disease as common as hypertension and with so little else to compete with it.

In 1932 Goldring and Chassis reported on their trial of the drug and concluded that, because of the uncertainty regarding proper dosage and the fact that frequently there is slight if any difference between the amounts that produce therapeutic and toxic effect, there is no place for it in the rational treatment of hypertension.

Following this report and largely because of their attitude the use of thiocyanate was generally abandoned. But in 1936 Barker reported that he had treated 45 patients with hypertension by sodium or potassium thiocyanate and had controlled the dosage by determinations of

the blood cyanate. He claimed that the reduction in the blood pressure and the relief of symptoms obtained in 35 of the 45 roughly corresponded to the level of the cyanates in the blood. He found the optimum therapeutic level between 8 and 12 mg. per hundred cc. and that toxicity begins to appear at from 15-30 mg. The method suggested for the determination of the blood cyanate is simple and takes less than 10 minutes to perform.

Following this report there was a renewed interest in the drug and numerous reports have appeared with conflicting conclusions:

Recently Goldring reporting further on his experience with the drug stated that thiocyanate should not be administered in hypertension because, apart from its toxic effects, its influence is not striking in either the frequency or extent of blood pressure reduction and that almost any medical or psychotherapeutic measure may be expected to yield results equally effective and with no element of danger.

On the other hand, we have the published opinion of Irvine Page who is an investigator of comparable experience who states that "There is no doubt that since Barker's introduction of the control of thiocyanate dosage by estimation of the thiocyanate content of the patient's blood, this drug has assumed a place of importance in the treatment of arterial hypertension."

The positions taken by these two important investigators in this field are absolutely opposite and seem entirely irreconcilable. It leaves the practitioner who is seeking some guidance in a quandary. Yet, if the published data of these two be carefully examined, it will be seen that their findings are not very different and that only their judgments are conflicting.

Goldring has considered the drug effective only if the pressure fell to 165 systolic and 100 diastolic; but in some of his cases there were marked falls in both systolic and diastolic pressure, yet, because the drop was not to the level arbitrarily set, the drug was declared ineffective. In spite of this Goldring and Chassis found that the pressure was effectively lowered in 31 per cent of the cases studied. They showed also that the hypotensive effect persisted from 7 to 110 days after the discontinuance of the drug. Almost invariably a fall in blood pressure was accompanied by subjective improvement.

The most disconcerting fact brought out by Goldring and Chassis was the frequency of toxic manifestations (13 out of 50 patients) and

the fact that two of these patients died. Barker maintained that such fatalities may be avoided by controlling the dosage by estimation of the level in the blood and the experience of others seems to bear this out. The fact remains, though, that occasional patients become toxic with a level of only 6 or 7 mg. per cent, while others tolerate a level of 20 mg. without untoward symptoms. The level which has seemed most likely to be effective without giving rise to toxic symptoms is the range between 8 and 12 mg. But in any case the optimal level must be carefully sought by gradually increasing the dosage to the point of effectiveness and lowering the dosage with any evidence of toxicity or sharp rise of the thiocyanate in the blood.

The toxic symptoms which should be carefully watched for are weakness, persistent bitter taste, anorexia, nausea, itching, dermatitis, purpura, mental confusion and disorientation. Evidence of toxicity is not likely to occur unless the concentration of the drug in the blood exceeds 15 mg. It is most likely to occur in older patients who have had severe hypertension for many years and in whom renal function is poor.

The patients most likely to be benefited are those under 60 who have shown no evidence of congestive heart failure, renal failure or cerebral change. Whether or not the anginal syndrome should be regarded as a contraindication is not clear but the probability is that lowering the blood pressure in these patients may increase the number and severity of their attacks.

Various methods of giving the drug have been proposed. The method I use is to give a 3 grain enteric coated tablet morning and night. If at the end of one week the tension has not been significantly lowered I increase the dosage to 3 such tablets. When the symptoms have been relieved and the tension lowered to about 160 systolic, 100 diastolic, an attempt is made to maintain this improvement by a daily dose of 3-6 grains. If after six to eight weeks of trial no benefit is obtained, the use of the drug is discontinued.

The thiocyanate level in the blood is determined once each week, using the method proposed by Barker. We have found this adequate for office practice even though it is difficult to make an exact reading. In hospital practice we use an accurate standard and make the determination with a photoelectric colorimeter. We try to keep the level between 8 and 12 mg. A level of 15 mg. should never be exceeded although many patients tolerate 20 mg. without untoward effect.

* One might sum up the essential facts about the use of thiocyanate in hypertension by saying that: (1) it is the only drug which we have that in a considerable number of cases (one third to one half) causes a drop in tension which is of more than transient duration; (2) in about an equal number of patients it gives relief of distressing symptoms; (3) it may often cause toxic symptoms of minor character and rarely (6 reported cases) death; (4) it requires careful, close observation and skill in adjusting the dosage for each patient and determining a maintenance level which is effective but not toxic; (5) the determination of the drug level in the blood has been invaluable in controlling the dosage and preventing severe toxic reactions.

It is far from an ideal drug but when I am confronted with a patient whose tension is tending toward 250 or more I find it difficult to stand by and not use this drug since there is nothing else that is equally effective.

SURGICAL TREATMENT

Having done everything that medical treatment has to offer (having tried rest, sedation, psychotherapy, thiocyanates, etc.) sooner or later in a few cases when the disease shows signs of rapid progression and complete refractoriness to any therapy, the question of surgical intervention will arise. The public is now asking for authoritative information about it. It is up to the practitioner to familiarize himself with the new developments in this field, for it is he who finally decides which patients should be considered for this type of treatment.

The various surgical procedures that have been proposed are based upon the supposed relationship between hypertension and the adrenal gland, the sympathetic nervous system and the peripheral vascular system. The operations are of two general types: (1) The one type is directed at decreasing the secretion of the adrenal glands by resection or denervation; (2) the other attempts to paralyze the vasomotor control over large vascular areas.

Adrenal Gland: Two operations have been proposed based upon the concept that hypertension results from a hyperfunction of the adrenal gland: (a) Total denervation of the gland was done for the most part by Crile and failed to give satisfactory results; (b) the other procedure done on the adrenal gland was subtotal resection. The rationale of this procedure was similar to that in the treatment of exo-

phthalmic goiter. It was assumed that if the subtotal removal of the thyroid gland improved hyperthyroidism through the reduction of thyroid secretion, the subtotal removal of the adrenal gland should, by the reduction of adrenalin secretion improve hypertension. The operation has consisted in the partial removal of one gland, the total removal of one gland or the subtotal removal of both glands. While some reports in the literature are favorable, on the whole the results have been unsatisfactory.

To summarize the relationship between the adrenal gland and essential hypertension it may be said that there is no conclusive evidence either clinically, with patients, or experimentally, with animals, that shows a causal relationship; and that the surgical treatment based on this concept is for the most part unsatisfactory.

The possibility that chronic spasm of the splanchnic arterioles (by whatever mechanism this may be mediated) may be the basis of essential hypertension has been the basis for several operative procedures upon the sympathetic nervous system. There is evidence that suggests that the splanchnic vessels constitute an important flexible reservoir which governs the level of arterial pressure and that in essential hypertension the elevated blood pressure is due in part to constriction or loss of elasticity of the splanchnic vessels. Interruption of what is believed to be the chief vasoconstrictor nerve supply may then cause a reduction of arterial blood pressure. Based upon this idea are several operations which are intended to interrupt the sympathetic control of the splanchnic vessels. These operations include the resection of the splanchnic nerves above or below the diaphragm combined with removal of the lower dorsal or upper lumbar sympathetic ganglia; the removal of the celiac ganglia; and the division of the anterior nerve roots of a defined region of the spinal cord.

Three types of operations have been used: The supradiaphragmatic, the infradiaphragmatic and the transdiaphragmatic.

Supradiaphragmatic operation: Peet reported on 350 consecutive cases operated upon by him from 1933-1940: operative mortality, 3.4 per cent; 86.6 per cent had postoperative relief of major symptoms, especially headaches; 81.3 per cent had improvement or complete relief of incapacitation; 51.4 per cent had significant reduction in blood pressure. Approximately one-half of these patients had pressures reduced to normal or markedly reduced. Improvement in the ophthalmologic.

cardiac and renal status following operation varied from 45-70 per cent of the cases studied. Prognosis was better in females than in males. The most favorable results are obtained in the age group below 30. After this period the age seems of minor importance.

The infradiaphragmatic operation has been employed chiefly at the Mayo Clinic. The operative mortality is no higher than with the supradiaphragmatic operation. Allen and Adson have made the most important study of its effects in a group of 224 patients; 13 per cent are classified as good results, as judged by prolonged reduction in blood pressure, 18 per cent as fair, 39 per cent as temporary and 30 per cent as poor. All the group 4 hypertensives (malignant syndrome) did poorly. Although arterial pressure returned to its preoperative level in most patients, still many of them remained free of symptoms, especially headache, dizziness, fatigue, thoracic pain and shortness of breath.

The transdiaphragmatic operation was devised by Smithwick of Boston who has reported the results as follows: 58 patients were operated upon with 2 deaths following the first stage of operation. The results are derived from the study of 26 of these patients who had been studied from four months to two years. Six out of 8 group 1 hypertensives showed a significant change (by significant is meant a fall in arterial pressure to below 140/100 or systolic or diastolic was normal), 5 out of 5 in group 2, 2 out of 6 in group 3 and 4 out of 7 in group 4 (malignant). Smithwick has had a large experience with other types of sympathectomy and is in a position to evaluate with authority the results of operation. It is, therefore, of importance that he considers the results of the newer technique clearly superior to the older ones.

These operations on the sympathetic nervous system were designed to accomplish the following: (1) Denervation of a large vascular area, approximately the entire area below the diaphragm, and the denervation of the vessels carrying blood to the kidneys in order to eliminate the effects of vasospasm on the circulation in the denervated region; (2) to create a reservoir in the denervated vascular area when the undenervated vessels went into spasm; (3) the thorough denervation of the adrenal glands, by interrupting the sympathetic fibers before they entered the capsules of the glands (this should eliminate the central influence in producing excessive secretion and the flooding of epinephrine under emotional stress); (4) the thorough denervation of

the arteries which supply the kidneys should increase the circulation of the kidneys and might aid in elimination of metabolic products which if present and retained might produce pressor effects on the arterial tone.

The selection of patients for operation is probably as important in determining the end results as the actual operative procedure. For the most part operation should be reserved for patients whose hypertension, if mild, is definitely progressive in spite of medical supervision, and for those who have severe hypertension which has not responded to medical treatment.

There are no infallible criteria for selecting patients at the present time. However, the patients whose blood pressures decrease to normal or nearly to normal as results of rest or sleep, or oral administration of 3 grains of sodium amytal every hour for 3 successive hours, or the slow, intermittent intravenous injection of a 5 per cent solution of pentothal sodium to produce light anesthesia, receive the greatest benefit from operation. A satisfactory response to these tests indicates that the arterioles offer increased resistance to the flow of blood largely by virtue of functional, hence reversible, changes and not as a result of organic, hence largely irreversible, changes. Conversely, those patients whose blood pressures do not decrease satisfactorily as a result of these measures, benefit from operation, as a group, to a substantially less degree than do those whose pressures are still labile. One need not consider as contraindication to operation sclerosis of the retinal arteries, moderate enlargement of the heart, inversion of the T waves in EKGs, albuminuria, slight reduction in renal function or cerebral vascular accident from which recovery has been satisfactory. However, it is not advisable to operate on patients who have congestive heart failure, marked renal insufficiency, advanced arteriosclerosis, or angina pectoris. Perhaps as experience increases, even some of these patients may be considered suitable for operation. About 80 per cent of cases were benefited. Blood pressure in 45 per cent was not reduced.

To summarize the status of the surgical treatment of hypertension one would be justified in saying that lowering of the blood pressure has been shown to follow in a significant number of cases but that it has not been shown to be permanent in all; that improvement in the subjective and in some of the objective manifestations of the disease has been even more frequent. This has been especially true of the headaches.

in which a striking improvement is usually noted. In some cases improvement in the eye grounds has been noted, with disappearance of papilledema, hemorrhage and exudates. Which of the operative procedures will eventually be shown to be most effective cannot now be foretold; but the trend seems to be toward the more extensive operations such as the Smithwick.

RENAL EXTRACTS

A number of investigators have claimed favorable results from the administration of renal extract. The rationale for its use has been summarized by Grollman, Williams and Harrison as follows:

1. Tigerstedt and Bergman showed that renin induced a greater rise in blood pressure in nephrectomized than in normal animals. They attributed this difference to failure of the nephrectomized animals to excrete the pressor substance. In repeating their experiments Merrill, Williams and Harrison noted that the increase in sensitivity did not appear immediately after nephrectomy but only after a number of hours had elapsed. This led them to suspect that normal renal tissue might form some substance which was distributed in the body and which had the property of limiting the pressor effect of renin.

2. Further indirect evidence for the existence of a renal antipressor substance was furnished by the experiments of Blalock and Levy, who showed that in an animal with unilateral ischemia, removal of the normal kidney resulted in a marked rise in blood pressure.

3. Additional support for the existence of an antipressor substance was furnished by experiments in which it was shown that extracts of normal kidneys tended, on standing, to lose their pressor property more rapidly than did similarly prepared extracts of ischemic kidney of the same animal.

4. Another piece of indirect evidence for the existence of a humoral antipressor substance is the observation that hypertensive pregnant animals commonly develop a well marked decline in blood pressure during the last part of pregnancy and that the blood pressure increases to its previously elevated level following delivery. It would be difficult to account for such a sequence of events except by assuming that the fetus or the placenta forms some substance capable of reducing the elevated blood pressure of the mother.

The observations which have been cited all suggest that the kidneys

elaborate some substance which has the property of inhibiting the pressor effect of certain agents, including the renal pressor substance renin. Direct evidence of the validity of this hypothesis was obtained when it was found that extracts prepared from the kidneys of various animals did diminish the sensitivity of rats to renin and certain other pressor substances.

Extracts containing this antipressor substance were then administered to animals with experimental hypertension by Grollman, Williams and Harrison. They found that there was in these animals a decline in blood pressure. These same investigators then administered the extract orally and parenterally to a small number of patients with hypertension. In most of the subjects a decline in blood pressure occurred. However, they have refused to draw any conclusions as to the therapeutic effect in patients. They feel that the drop in blood pressure may be spontaneous, though this is unlikely; and that the subjective improvement may be due to suggestion.

Page and his co-workers have reported results in animals and patients which are essentially the same.

On the Third Division at Bellevue Hospital Goldring and Chassis have been testing renal extracts on two cases of essential hypertension and on two cases of hypertension due to chronic glomerulonephritis. The daily dose has been the amount of extract obtained from 50 kilograms of beef kidney. This has been given by mouth for several months. There has been no significant fall in the arterial pressure in any of them.

To summarize the present status of therapy by renal extracts, one might say that, though experimentally in animals they have shown some degree of effectiveness, in many they have been entirely ineffective when given by mouth. When given intravenously they have been effective in lowering the arterial tension but only when the treatment has been associated with a general systemic reaction usually with fever. This type of reaction is not specific for renal extracts, and similar effects may be obtained by the intravenous injection of any foreign protein such as typhoid vaccine. From the standpoint of the clinician the renal extracts have nothing to offer at this time.

AMINE OXIDASE

Another medical treatment is based on the theory that ischemic renal tissue, being deprived of adequate oxygen, fails to deaminate the

amines and since the amines are pressor substances, their accumulation in the blood results in hypertension. It has been suggested, therefore, that amine oxidase be given to correct this. Tyrosinase has been tried by some and quinones by others. In experimental hypertension in animals the effects have been striking but the evaluation is subject to the same difficulty as with renal extracts in that the pyrogenic reaction, occasioned by the treatment in itself, could account for the lowering of pressure. From the clinical standpoint this method has no value.

PSYCHOTHERAPY

Finally, a word about psychotherapy in these patients. Those who have been stressing the psychosomatic aspect of the disease believe that in some cases the hypertension arises because of suppressed aggression or rage. I have spoken to several psychoanalysts who tell of cures accomplished when such a neurotic mechanism was removed. Whether this is true or not, I do not know but no one can doubt the value of some form of simple psychotherapy. Much can be accomplished by a friendly understanding and encouraging chat in which the physician explains the natural history of the disease, stressing its long course, directing the attention away from the blood pressure and even pointing out that it may be better not to lower it.

If any one doubts the value of psychotherapy, let him recall how often patients feeling well have consulted him, been told that the blood pressure had gone up a few points and then had left the office low in spirits, weakened and depressed. Conversely, how often do these patients, being told that their blood pressure had dropped, become elated and relieved of many of their symptoms. We must maintain for the benefit of these patients an optimism which alas! we often do not feel but which, even if simulated, may be used as an effective therapeutic measure.

SUMMARY AND CONCLUSION

1. All cases of hypertension should be studied to rule out primary renal disease.
2. This is especially important because of the possibility that the primary renal disease may be unilateral and amenable to surgery.
3. In cases of essential hypertension one should bear in mind that the disease may be latent at birth and develop gradually over several

decades; hence the importance of studying each case in order to obtain a more accurate orientation and a better judgment of the outlook.

4. In most cases it is not necessary to try to reduce the arterial tension and it is not even clear that this is always an unmixed good.

5. Thiocyanate is the only medication that in any considerable percentage of cases lowers the arterial tension.

6. The cases in which surgery is indicated are few and the benefits still problematical but this form of therapy is receiving increasing attention.

7. Treatment by renal extracts and by amine oxidase has a reasonable background but practically these methods have been unimpressive.

8. Psychotherapy has a place in the treatment of every case of hypertension. Whether or not it is useful in removing some neurotic mechanism that may be related to the development of hypertension, it can always help the patient adjust to the limitations imposed by the disease.

SEQUELAE AND COMPLICATIONS
OF CONVULSIVE SHOCK THERAPY*

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I^N THE evaluation of a therapeutic measure we balance the therapeutic efficacy and urgency of the treatment with the potential risks and health hazards of such treatment. In view of the increasing popularity and widespread use of convulsive shock treatment for various psychiatric disorders it would seem justified that we consider in some detail any undesirable or untoward effects resulting from these treatments. Our information relative to such effects is drawn largely from observations and follow-up studies carried out on about 300 patients and also to a substantial degree from the experiences and reports of other investigators.

Of course, the most serious complication is death. This is only rarely encountered and in fact in well selected and well prepared cases is never encountered. Thus far there have been no mortalities directly attributable to the treatment in over 500 patients treated at the Psychiatric Institute.

Kolb and Vogel,¹ in an analysis of figures from several hundred institutions in the country listed only four deaths as attributable to electroshock treatment in 7,207 cases, a death rate of 0.5 per thousand. This compares with a death rate of one per thousand in metrazol-treated cases and 6 per thousand in insulin-treated material. In an analysis of fatalities throughout the United States, up to June 1942, Doctors Ebaugh, Barnacle and Neuburger² found ten deaths, two of them occurring in their own experience. However, some of these deaths apparently were not directly or immediately the effect of the induced convulsion since the condition responsible for the exitus occurred some months after treatment. More recently Impastato and Almansi,³ in a review of the literature, reported 8 electric shock deaths in an estimated 11,000 cases. It is important to note that in 4 of these

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cases death was attributable to cardiac complications; the others died of pneumonia, pulmonary edema and post-convulsive respiratory arrest, while in one case the cause was not definitely ascertained.

Although one obtains the impression that cardiovascular involvement precludes the use of convulsive therapy it has been our experience and the experience of many others that individuals with varying degrees of cardiovascular disease, with or without abnormalities in the electrocardiogram, ordinarily tolerate convulsions well, providing the disease is not too acute or severe. Most cardiovascular disturbances occurring after electroshock are transitory, usually disappearing within 5 to 30 minutes and generally consisting of bradycardia, extra-systoles and sinus arrhythmia. In a few instances cardiac collapse occurred immediately after the convulsion with the patient exhibiting marked pallor, weak, slow and irregular pulse and low blood pressure. These cases recovered spontaneously after each treatment. Although it has not occurred in our experience, cardiovascular reactions have been reported where apparently cardiac failure appeared some time after electroshock, perhaps 20 or 30 minutes later and subsequently cleared up. Some investigators have reported complications in patients with valvular disease. Ziegler⁴ mentions a case of old endocarditis which flared up after convulsive therapy, while another case with rheumatic chronic valvular disease reported by Kline and Fetterman⁵ showed temporary cardiac failure about 20 minutes after the first convulsion and recovered in about 30 minutes subsequently. The cardiac deaths earlier referred to have been caused by dilatation of the heart, myocardial damage, ventricular fibrillation and coronary occlusion. Evans⁶ has reported the use of electroconvulsive therapy in patients with coronary disease, auricular fibrillation and hypertension with no ill effects on the course of the heart disease.

We have routinely employed electrocardiograms prior to shock treatment and have been exceedingly cautious in proceeding with the treatment where the EKG shows substantial cardiac disturbance, where there has been a history of rheumatic heart disease with clinical signs of vascular damage, or a history of previous coronary disturbance. Some believe, however, that a cardiac decompensation is the only absolute contra-indication to shock therapy.

A number of interesting observations relating to blood pressure changes have been recorded in connection with shock therapy.

Menninger⁷ reported the case of a patient who developed hypertension during a course of metrazol shock treatments and which persisted over four years afterwards, although the patient had had a normal pressure prior to treatment. I might mention that two of our own cases, one of whom received metrazol and the other electric shock therapy also exhibited a hypertension varying from 160 to 180 mm. of pressure systolic, some months after therapy. One of the patients was a 40 year old agitated depression who showed complete remission of psychiatric symptoms with treatment, even after a period of 3 years. The other patient was diagnosed as a catatonic schizophrenic who showed excitement features during the illness and became much improved subsequent to treatment. Both patients had normal tensions prior to treatment. It should be noted, however, that the blood pressures were not routinely taken in all patients after shock therapy, but were taken in only a relatively small number of cases and in a few who complained of dizziness or headaches as these two patients did. We, therefore, do not know whether more patients developed an increased pressure. On the other hand we have no control group of psychiatric patients of a similar type who received no shock therapy and who were subsequently studied for tension changes so that it is quite possible that the increased pressure in the two cases might have occurred whether shock therapy was given or not. It is known that the blood pressure becomes elevated during and for a short period immediately after a seizure but then soon drops back to the pre-seizure level, or to an even lower pressure than prevailed before the treatment. Very often patients with increased pressures prior to therapy, in some instances exceeding 200 systolic, exhibited a substantial lowering of the tension as their clinical condition improved; it is probable that this is more frequently the case rather than an elevation of blood pressure after therapy.

There is some question regarding the possibility of rupture of vessels during the seizure. Although subconjunctival hemorrhages are occasionally noted, retinal hemorrhages have not been observed. We have had no occasion to suspect the presence of intracranial hemorrhage. Studies of spinal fluids immediately after a convulsion in metrazol-treated patients revealed no evidence of subarachnoid bleeding. We might mention the case of Ziegler⁴ where the patient had a subarachnoid hemorrhage 2-3 years prior to treatment and showed no untoward effects with shock therapy.

With respect to pulmonary and respiratory complications, the most frequent and consistent occurrence is apnea, which is present during the actual convulsion and which persists for short varying periods after the seizure, generally not exceeding 30 seconds. As mentioned above, there has been only one case reported in the literature of respiratory arrest which resulted in death. Ordinarily, a few applied artificial respirations are sufficient to bring on spontaneous respiratory movements in a prolonged period of apnea.

Occasionally one observes a post-convulsive stridor which might be caused by nasal obstruction and blockage of the air passage through the mouth by means of the gag. This is readily cleared by manipulating the gag so as to secure an air passage through the mouth. On frequent occasions, we have found that the stridor can be relieved by applying firm pressure to the jaw upwards and slightly retracting the head.

We have experienced only one instance of pneumonia which occurred within 36 hours after the patient received a convulsion. This patient cleared up with the use of sulfadiazine in a few days and after a two-week interval, convulsive therapy was reinstituted. After three treatments she again developed a pneumonic consolidation in the opposite lung, which again cleared up rapidly with sulfadiazine. There have been reported in the literature instances of pneumonia occurring in association with insulin shock therapy, but this is a rare occurrence in convulsive shock. With the exception of one case of lung abscess reported by Kalinowsky,⁸ no other such complication has been mentioned in the literature. We have encountered no such cases in our own material. It may be noted that abscesses are not too uncommonly observed in insulin treated patients.

We might mention that in a few instances where patients had mild upper respiratory infections without elevation of temperature, we have observed no untoward effects with the administration of shock, although we generally prefer to postpone treatment in these instances.

The question as to whether convulsive treatments activate or aggravate tuberculous lesions is not yet fully decided. A number of studies have been reported for metrazol-treated cases,^{9, 10, 11} where tuberculosis is reported to have been activated and also where there was an indication of an increased incidence of tuberculosis in the treated material. We are not aware, however, that any of our own patients have shown any reactivation of tuberculous lesions. At least four of our group gave

histories of active tuberculosis at some time within a 15-year period prior to shock therapy, which required prolonged medical care and bed rest in order to effect healing of lesions. None of these patients showed a reactivation of tuberculosis. An additional patient whom we treated had a therapeutic pneumothorax at the time of treatment but she went through the course of shock therapy without ill effects and subsequently showed improvement in her pulmonary condition concomitant with the improvement in her psychological status. Smith¹² administered convulsive therapy to an agitated, middle-aged female who at the time of the treatment exhibited active tuberculous lesions of several years duration in both lungs. There was about 200 cc. of fluid in the left pleural sac and pneumonic consolidation in the right lung. She was running a daily elevation of temperature of about 1-2 degrees. However, this patient showed no untoward effects in a series of 20 electro-treatments. She improved both in her psychiatric status and in her pulmonary condition. However, we cannot negate the possibility that in these cases complications might occur with shock treatment, and that it is necessary that we judge each individual case on its own merits and balance the severity of the psychiatric symptoms with the severity of the pulmonary tuberculosis.

We have not noted any serious or severe gastro-intestinal complications in our material, although Ziegler⁴ reports a patient with gastric ulcer which bled after a convulsion. Post-treatment nausea is quite frequent, but generally disappears within a half-hour after shock. Vomiting rarely occurs. Biting of the tongue and lips may sometimes occur, although with ordinary care and precaution in the handling of the mouth gag, this can be prevented. It is advisable, incidentally, that all easily removable dentures be taken out of the mouth before each shock treatment.

Complaints referable to the muscles are quite frequent, but not serious. After the first convulsion the individual usually complains of cramps or soreness in the muscles of the limbs and back. Very often the soreness is most marked close to or between the angles of the scapulae, but no local tenderness is present as a rule unless there are other complicating features such as vertebral fracture or tearing of the muscle. The latter is only rarely encountered. Savitsky¹³ mentioned a tear in the deltoid muscle which healed uneventfully. The myalgias are observed more frequently in well-built muscular individuals than in other types

of persons. It is not too uncommon for patients to complain of an achy feeling in the muscles of the chest on inspiration, after a course of shock treatments. This usually subsides very soon after the treatments, although in a few instances this feeling persisted for some months after therapy and then disappeared.

The skeletal system is commonly involved in complications, with vertebral compression fractures a relatively frequent occurrence. The region usually involved is the midthoracic spine. The fractures vary in severity, at times being quite marked but in the majority of instances being only mild in degree. It appears that maintaining hyperextension during the treatment reduces the incidence of such fractures. Statistics regarding the incidence of vertebral fractures vary widely. Impastato and Almansi³ in examining the literature found that there were 39 cases of fracture of the thoracic spine reported out of a total of 1750 cases, or an incidence of 2 per cent. Polatin et al¹⁴ had previously reported an incidence of approximately 43 per cent in metrazol-treated cases with extension and Horwitz,¹⁵ in a study of electric shock cases where hyperextension was employed found approximately 20 per cent fractures. It is to be noted, however, that in the studies by Polatin and by Horwitz which were conducted at the Psychiatric Institute, the patients were x-rayed routinely after termination of treatment. It is our impression that this was not done in the material reviewed by Impastato, where it is more likely that only those cases were x-rayed which showed suggestive symptoms of possible fracture. It has been a frequent experience in routinely x-raying patients after the end of therapy, that many cases of fracture are observed where the patients have no symptoms at all. Even in the severe compression fractures, where 2 or 3 vertebrae may be involved, symptoms are surprisingly mild and do not generally persist for more than several days after the last treatment. In a few instances, however, back pain and local tenderness on deep pressure have continued for several weeks. In 2 cases where back pain persisted for some months the patient exhibited no fractures and it was believed that the symptoms might have been related to some tearing of muscle or of other soft tissue structures. It has been the general observation that these fractures heal well even when multiple, without splints or immobilization and without any residual or subsequent neurologic or physical findings. If fractures of the vertebrae occur early in the course of treatment, the question always arises as to whether the shocks should

be continued. This depends, we should say, to a large extent upon the severity of the psychiatric picture and the extent of the injury. If the injury has not been too severe and psychiatric symptoms are expected to show good remission with further treatment, it has been our custom to go ahead with treatment. One could perhaps employ curare in such instances to lessen the severity of the contractions.

We have encountered one instance of fracture of the neck of the femur. Similar fractures involving not only the femur but also the other long bones and also the hip bones, clavicles and scapulae have been reported. These are very rare complications and perhaps can be prevented if the patient is not permitted to swing about wildly during the convulsion. However, when one of these fractures does occur, they are generally more troublesome and difficult to handle than are the fractures of the spine. Since they are more prone to occur in elderly people, the fracture is likely to be a rather disabling one.

Curare has been utilized for softening the severity of contraction of the muscles during the seizure in an attempt to diminish or eliminate the incidence of fractures. Some have advocated the extreme point of view that this drug be used as a routine procedure in combination with convulsive therapy. Bennett¹⁶ has advocated this viewpoint, and has reported a marked diminution or absence of fractures in the curarized patients. Cash and Hoekstra¹⁷ administered 995 combined curare-electroshock treatments to 139 patients and reported no traumatic complications in this group, but reported one death. We might mention the observation of Impastato and Almansi³ that 50 per cent of the 8 electric shock cases so far reported in the literature to have died as a result of electric convulsive therapy received curare prior to treatment. This may be significant when we regard the relatively few individuals who have been treated by preliminary curarization in electric convulsive treatments. We have hesitated to use this drug routinely in combination with electric shock and have the impression that the danger attendant with the routine administration of curare plus the undesirable psychological effects it seems to have in many patients is not sufficiently compensated for by its minimizing effect on the severity of the muscular contractions and the resulting diminution of fracture incidence.

Dislocations of the jaw sometimes occur but they are easily reducible immediately after the convulsion. These dislocations usually can be prevented by holding the jaw firmly upward at the time the shock

is administered and also during the seizure. Most frequently the jaw is dislocated at the onset of the seizure when the mouth is suddenly and widely opened and the mandible is thrust forward.

There have been very few objective or even subjective neurological manifestations as complicating features of convulsive therapy and none of these have been of a very serious or incapacitating nature when the individuals have been clinically normal prior to treatment. Occasionally patients may complain of numbness and tingling sensations in the limbs but this disappears within several days as a rule. In a few instances patients have complained of tinnitus and buzzing in the ears for several days following treatment. One patient who showed complete remission complained of continuous buzzing for about 2 weeks. Three patients have complained of attacks of dizziness, in one instance accompanied by fainting spells. These attacks would come on suddenly at any time of the day, and almost simulate a Ménière's syndrome. One of these patients, who received metrazol about three years ago, exhibited congenital nystagmoid movements prior to treatment. A second patient showed signs of cerebral arteriosclerosis and complained of mild dizziness prior to therapy while the third patient was apparently suffering from a concussion syndrome in addition to her psychotic state. These latter two received electro-shock. The first and third cases have continued to show marked dizziness while the third exhibits in addition, fainting spells. The patient with arteriosclerosis has cleared up. It may be mentioned, incidentally, that in all three cases electroencephalograms had returned to normal after the treatments in spite of persistence of symptoms.

Of all the patients who received convulsive therapy two have developed spontaneous seizures. These occurred some weeks after the last treatment. Electroencephalograms had been taken prior to therapy, and in both instances revealed significant abnormal features. Electroencephalographic tracings taken after treatment continued to maintain marked abnormal features. It should be stressed that no patient with a normal electroencephalogram has developed any spontaneous convulsions. It appears that the two patients who developed post-treatment seizures and who, incidentally, presented no history of previous attacks, had latent convulsive tendencies as evidenced by the electroencephalograms. It is reasonable to assume that these tendencies were reinforced by shock treatment. We cannot subscribe whole-heartedly to the

opinions of some who believe that shock can be given with impunity to epileptics. This entire question is to be taken up in more detail in a separate report.

Spotnitz mentioned that metrazol-treated patients exhibited a persistent impairment of gustatory and olfactory perceptions. We have not been able to confirm this by gross clinical means nor have we noted anything in the literature regarding this, but it is possible that finer testing might bring out some impairment in these sensory spheres.

Other neurologic complications have been reported in the literature. Impastato³ quotes Trampler and Reisner as having reported a case of aphasia; another of brachial plexus neuritis and another of acute parkinsonism, following electric shock treatment. However, the possibilities of such complications appear to be extremely remote.

The question as to whether actual histopathologic changes occur or persist in the brain is subject to controversy. Some have reported capillary hemorrhages, gliosis and neuronal changes in experimentally produced convulsions in animals,^{18,21} while others have denied these findings.^{22,23} We have studied a series of monkeys who received a "course of electrical shock treatment" similar to that received by humans and have found no significant histopathologic alterations.²⁴ Of course one could always argue that a normal clinical status or at least a socially adaptable individual with a little brain pathology is preferable to a psychotic patient with no demonstrable brain changes.

Electroencephalographic tracings have been studied extensively in connection with convulsive shock.²⁵⁻²⁹ The changes reported have been found to be largely reversible. However, in a few instances, particularly in those patients who received many treatments (exceeding 12 convulsions within the course of a month or six weeks), the electroencephalogram still showed abnormal features a year after treatment.²⁸ It should be emphasized, however, that the presence of abnormalities in the electroencephalogram is not necessarily equated with histopathologic changes in the brain which could necessarily be demonstrated by the usual techniques. It is problematic whether shock therapy should be administered in patients showing certain types of abnormal electroencephalograms. This matter has been investigated by us and will be presented in a separate communication.

Psychologic changes have been very frequently observed in patients subjected to shock treatments. The most striking complicating feature

is the memory defect. This is noted early in the course of treatment and with increasing number of treatments becomes more pronounced and more persisting. The memory defect is both retrograde and antero-grade and is somewhat "lacunar" or spotty in type. It has been suggested by some that the patient forgets those things which he wants to forget or which have been the most sensitive or traumatic for him. We do not believe there is sufficient evidence for this opinion. As a rule, the memory defect disappears or markedly diminishes after a few weeks, but occasionally the patient still complains of slight memory loss for several months subsequent to treatment. In two instances the patients complained of memory impairment for as long as a year after therapy. However, the disturbance from the clinical point of view is relatively slight. A number of attempts to study this memory defect have been made by utilizing objective psychologic tests. Studies conducted by Zubin³⁰ of the Psychiatric Institute in which recall, relearning and recognition were tested, led him to believe that electric shock treatment does not in any way destroy memory, but simply disorganizes it. In other words, the memory traces are not lost, but are temporarily dissociated. He also concluded that the learning and retention process is only very temporarily affected since no ill-effects are noted in the post-treatment period. However, extensive testing of the memory over a prolonged period of time subsequent to shock was not carried out. It should be borne in mind that the control memory tests were given to psychiatrically ill patients and that the results were then compared with those obtained when the patients had received shock and were possibly in clinical remission of symptoms. In spite of this possible source of error, Zubin's results are very much in accord with our own clinical impressions.

There has been some question as to whether the intellectual level is affected but clinical observation of these patients over a period of time has given no gross evidence of actual intellectual deterioration which could be definitely ascribed to shock therapy. Nevertheless, there is certainly a need for more objective psychometric testing of these patients.

An evaluation of actual personality changes was made with the use of the Rorschach test. It is interesting that the patients exhibited an organic type of change of a diffuse type within the first hour subsequent to shock treatment, but after this the Rorschach analysis illustrates

the same personality features as were exhibited by the individual prior to the treatment even though he had no recollection of having been subjected to this procedure before shock. In this connection it should be stated that patients show varying degrees of confusion as a result of the shock treatments. This is usually mild, with the degree of confusion depending largely upon the frequency and number of the treatments, but varying considerably from patient to patient. The confused state is essentially an "organic" type reaction, in which the patient may become disoriented for time, place or person, and exhibit memory defect, particularly for recent events. It is generally more pronounced in elderly or arteriosclerotic patients, but usually disappears within 1 to 3 weeks after treatment, lingering on only in the form of the memory defect mentioned above.

In the course of convulsive therapy, it is often observed that the symptoms of the illness, particularly where depressive and anxiety features are prominent, may be temporarily exacerbated during the first few treatments. This seems to be due, at least in part, to the patient's reaction to the memory defect, causing an intensification of anxiety and motor restlessness, and necessitating constant reassurance by the physician. However, with further treatment the anxiety and depression diminish substantially, but at the same time the memory defect becomes more pronounced. The patient, however, is no longer especially concerned with the memory disturbance, although is still well aware of it. At this stage or towards the end of the treatment the patient may exhibit a mild hypomanic or euphoric state, which in some instances persists for some weeks before levelling off. In older individuals it is deemed advisable to exercise some restraint over the hypomanic drives of the patient, particularly if there is an associated hypertension. Very often, too, judgment during this phase might be impaired and a certain degree of caution must be emphasized to the patient or family.

One or two miscellaneous points might be mentioned. In occasional instances, a patient may complain of amenorrhea subsequent to shock treatment, even though there may have been complete regularity during and prior to the illness. We have not noted any permanent or long-continued cessation of menstruation, however. It might be of interest also to mention that 2 cases of pregnancy were given convulsive therapy, both of whom were in the fourth or fifth months of gestation. One of these patients was delivered of a normal healthy infant at full

term. We were unable to follow the course of events in the second patient, but up to the seventh month, the patient appeared to be getting along very well in her pregnancy, with no untoward effects.

CONCLUSION

It appears reasonable to conclude that the possible complications which are entailed by the use of convulsive therapy are far outweighed by the therapeutic benefits resulting from such treatment in the properly selected cases. Where a physical illness or defect is present to the extent that it offers a substantial risk for shock therapy, it becomes necessary to balance this potential risk against the severity of the psychiatric illness and the chances of therapeutic benefit which could result from the treatment.

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AMICROBIC PYURIA.*

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I^N the last decade treatment of infections of the urinary tract has been fairly well standardized. Certain general principles of diagnosis and treatment have been laid down and are well known. To me, the most interesting part of the whole problem of urinary infections is its relative simplicity, for if the general physician and the urologist will approach the question of treatment with a few well-organized principles in mind, a large percentage of infections of the urinary tract may be cleared up early and completely before they have time to produce changes in the kidneys, ureters or bladder which materially complicate the problem.

It seems unnecessary to mention to a group of urologists that first of all, before treatment is undertaken, the presence of an infection of the urinary tract and the general site of the infection should be established. Each year my colleagues and I at the Mayo Clinic see a number of women patients who have been taking mandelic acid or one of the sulfonamides to the point of tolerance in an effort to eradicate an infection of the bladder and kidneys which actually does not exist. It is true that these patients have burning and frequent urination and pus in the urine. The administration of various chemotherapeutic agents, however, has produced little if any benefit. On questioning the patient it often is found that only voided specimens of urine were examined, and when a catheterized specimen is examined, it is entirely free of pus or organisms. In this group of cases the detailed examination and history suggest inflammation of the urethra, and cystoscopy frequently reveals chronic granular or cicatricial urethritis or both. Local treatment for a few days is usually of great benefit and the patient is relieved.

In men pyuria frequently can be proved to be of prostatic origin. Chemotherapy for this type of pyuria is of little value. Thus, when females have pyuria or other symptoms of urinary infection a specimen

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of catheterized urine must be examined and when males have these symptoms the two-glass test of urine should be done routinely before treatment is instituted in order to determine whether the infection may involve the kidneys, ureters, or bladder.

Having once established the presence of an infection of the kidneys, ureters or bladder, it is now of value to determine the type of organism producing the disease and the presence or absence of any primary or secondary contributing pathologic infection. By no means do I wish to infer that every patient suffering from an infection of the urinary tract should have a complete urologic examination, including urographic and cystoscopic studies. However, I do feel that because of the well-known efficacy of mandelic acid and the sulfonamides in eradicating uncomplicated infections of the kidneys, ureters and bladder the use of these drugs should not be continued indefinitely. If two courses of treatment do not bring about sterilization of the urine, then the patient is entitled to a complete urologic examination in order to ascertain the presence of any existing condition in the urinary tract, such as stone, stasis, tumor, and so forth, which is hindering the action of the drug.

The importance of the infecting organism has been clearly demonstrated, but a few words of repetition seem indicated. Simple Gram's staining of the urinary sediment should be done in every suspected case. Examination of slides after Gram's staining will divide the cases into two groups: the first, those with demonstrable organisms, and the second, those without demonstrable organisms. It will divide the first group further and indicate to the physician whether he is dealing with a bacillary or coccal infection and whether the organism is gram-positive or gram-negative.

It is the second and smaller group of cases without demonstrable organisms which I should like to discuss in detail in this paper, because I am certain that their existence is not fully appreciated by either the general physician or the urologist. All physicians were taught early in their training to consider sterile or amicrobic pyuria indicative of a tuberculous infection of the urinary tract. Undoubtedly, this is the usual cause but by no means does it account for all such cases. What then is the etiologic factor in these cases?¹⁻⁴ Is an ultramicroscopic organism or a filtrable virus the causative agent? Is bacterial invasion of the renal parenchyma present without any organism reaching the tubules and hence the urine? If such invasion occurs, are the cellular elements

in the urine the result of the inflammation produced by the liberated toxin? Another possibility is that the toxins liberated by foci of infection elsewhere in the body are excreted by the kidneys and produce the resulting inflammatory reaction. Ewert and Hoffman,⁵ Moore,⁶ and others in their writings suggest an ultramicroscopic organism or filterable virus as the most likely cause of pyuria without demonstrable organisms. Studies at the Mayo Clinic certainly cannot disprove this hypothesis but I feel that in a large number of cases foci of infection elsewhere in the body contribute to the etiology of the inflammatory reaction in the urinary tract, and unless these foci are eradicated, complete cure is difficult to obtain.

The duration of the disease varies. Originally it was my impression that it was present for months or even years in most cases but as ability to recognize it increased a number of patients have been seen early in their illness. The local symptoms are referred to the bladder and urethra and are usually severe—more severe, indeed, than those seen in the usual bacillary or coccal infections of the urinary tract. Dysuria and frequent urination with tenesmus are the rule. Sometimes there is hematuria and on occasions the distress reaches the point of stranguria. Systemic reactions are not common but in a few cases pain in the loin with chills and fever, general malaise, anorexia, and so forth have been noted.

The urine is loaded with cellular elements; leukocytes, erythrocytes and epithelial debris. Repeated Gram's staining and staining of the urinary sediment for acid-fast bacilli and repeated cultural studies fail to reveal any infecting organisms. The finding of so-called sterile pyuria, of course, should bring to the examiner's mind the possibility of a tuberculous infection and this condition must be ruled out by repeated use of stains to indicate acid-fast bacilli and inoculations of guinea-pigs. A large number of the patients suffering from such pyuria not due to tuberculosis have been submitted to an intensive anti-tuberculosis regimen which entailed an entirely unnecessary economic burden. Because of the occasional difficulty in finding the tuberculous organisms in stained slides of urine and the length of time required to carry out the guinea-pig test, a tentative diagnosis of tuberculosis is made. However, failure to find certain clinical signs of tuberculosis of the urinary tract should tend to exclude this condition even before the laboratory reports are received. These signs, however, generally are not known. Bumpus and Thompson³ have shown that in 80 per cent of

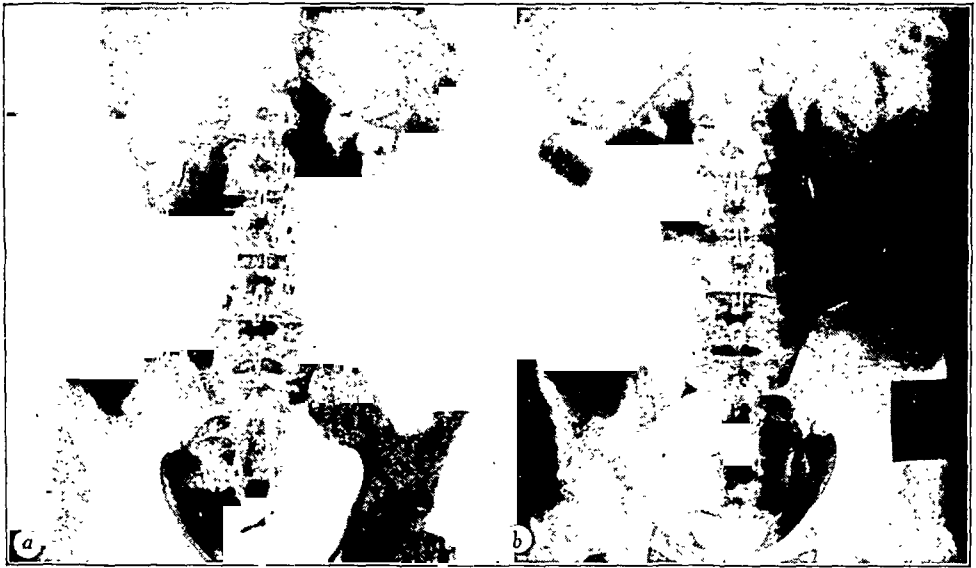


Fig. 1—Urograms in a case of amicrobic pyuria *a*, before treatment; dilatation of the renal pelvis and calices may be noted; *b*, after treatment.

the cases of tuberculosis of the upper part of the urinary tract the genitalia are involved also. In such cases the clinical findings are nodular and thickened epididymides, beaded pipestem vasa deferentia, or nodular prostate gland. The diagnosis of tuberculosis should never be made without corroborative evidence other than the apparently sterile pyuria and some suggestive cystoscopic or urographic findings.

Cystoscopic findings in cases in which non-tuberculous, sterile pyuria is present are a reduced vesical capacity, extreme irritability and diffuse involvement of the vesical mucosa with redness, edema and at times ulceration. These findings usually appear to be superficial, but in the cases of infection of long standing the deeper tissues seem involved as well. Ureteral catheterization almost always reveals bilateral renal infection of varying degree. One side may be involved to a greater degree than the other side. Renal function is rarely impaired except in the late stage of the disease.

Urography frequently discloses dilatation of the pelves, calices and ureters which is suggestive of an inflammatory origin, and in other cases the urographic findings are negative. Positive urographic findings may invite a certain pessimism with regard to prognosis but this should not be. Urograms made in the case of a young man (Fig. 1*a* and *b*) suffering from this type of infection of the urinary tract indicate the

change in conditions before and after treatment. The return to normal is frequently noticed if the disease is not too longstanding.

Experience during the last decade has taught a great deal regarding treatment of these conditions. Primarily it has been learned that the usual urinary antiseptics given by mouth are of little or no value. None of the sulfonamide compounds or mandelic acid is effective in relieving symptoms or reducing the pyuria. Local therapy if carried out intensively may be helpful but by no means is it as useful as in the infections with demonstrable organisms. In a few cases the infection is so severe that examination is required in the hospital, and continuous irrigating systems for vesical lavage must be employed. In these cases gradually increasing strengths of solutions of silver nitrate, beginning with a 1:10,000 solution and proceeding to a 1:1,000 solution, if possible, have been used with benefit. This type of lavage, however, is usually only a palliative measure. Most observers agree that the therapeutic weapon of choice in combating this disease is the intravenous use of an arsenical preparation. Improvement usually comes after the first or second injection in our experience.² This experience has been confirmed recently by Ewert and Hoffman.⁵ Occasionally a third or fourth injection may be required but this is not the rule. In my experience small doses of neoarsphenamine are just as efficacious as the larger doses, and I recommend 0.2 gm. for the first dose, followed in four to five days by a dose of 0.3 gm., with subsequent doses, if needed, given at the same interval and of the same size. Because of the excellent results which usually follow the administration of the arsenicals intravenously, it has been supposed that a spirochete might be the etiologic agent. However, Wildbolz⁷ has called attention to the fact that the Wassermann reaction on the blood for syphilis and examination of the urine for the presence of spirochetes by dark-field illumination always give negative results.

Having discussed the most important therapeutic procedure, I wish now to say a few words concerning what I believe to be a definite adjunct to treatment and in some cases a positive requirement. I always hesitate to suggest foci of infection as the reason for a urologic disorder. This hesitancy exists because of the difficulty of proof and also because I do not wish to encourage the indiscriminate removal of teeth or tonsils for infections of the urinary tract. However, in a large group of these cases in which initial improvement has been brought

about by the administration of the arsenicals, removal of any foci has produced a definite exacerbation of the symptoms with an increase in the urinary findings. This observation certainly seems to suggest a relationship. Furthermore, in a few patients who have recurrent trouble even after taking arsenicals, removal of foci has brought about a complete cure. Foci are important and should be borne in mind. The teeth and tonsils should be investigated carefully; the prostate gland should be examined and massaged if infection is found, or the cervix uteri should be carefully checked and treatment instituted if necessary.

REPORT OF CASE.

A white man, twenty-one years of age, registered at the clinic November 1, 1943. His main complaint was burning and frequent urination, hematuria, and extreme dysuria of four months' duration. Examination at home had revealed a bladder of small capacity, severe cystitis and definite reduction of renal function as shown by the excretory urogram. Early hydronephrosis was noted on both sides. Staining of the urinary sediment was reported to show acid-fast bacilli. Inoculations of guinea-pigs had not been made.

At the time of examination at the clinic the patient was wearing a urinal because of the extreme frequency and urgency. His tonsils were grossly infected and exuding pus. There was definite suprapubic tenderness and his prostate gland was tender on rectal examination. The genitalia were otherwise normal. The significant laboratory data revealed pus, grade 4, and erythrocytes, grade 4, in the urinary sediment but all the staining and cultures of the urine failed to reveal the usual invading organisms as well as the acid-fast organisms of tuberculosis. Visualization of both kidneys was delayed in the excretory urogram and there was dilatation of the pelvis, calices and ureters, grade 2. Cystoscopic examinations under pentothal sodium anesthesia revealed acute diffuse cystitis, grade 4, which was not suggestive of tuberculosis.

Continuous vesical lavage with 1:10,000 of silver nitrate was begun and continued for one week. The patient then was dismissed from the hospital and local treatment as described previously was carried out in the office twice daily. He was given one injection of neoarsphenamine and this medication brought about real improvement in his condition. Five days later a second injection was given with further improvement but unfortunately toxic erythema developed and further treatment of

this nature was impossible. His situation remained about the same for another week and tonsillectomy was advised. This was done and was followed by a definite exacerbation of all his vesical symptoms for two or three days. Local treatment was continued and in one week following tonsillectomy all symptoms had disappeared. The urine continued to show pyuria, grade 3, but with lavage and prostatic massage, the urine cleared up and the patient was dismissed as cured. An excretory urogram just before dismissal was entirely negative and cystoscopic examination gave negative results except for a few patches of redness over the trigone of the bladder.

COMMENT

The main concern of this paper is a condition which is becoming better known as time goes on. However, the frequency with which it is missed seems ample justification for considering it in detail. Careful studies of the urinary sediment and cultures of the urine, when possible, are of utmost value and should be carried out in all cases. The differential diagnosis between amicrobic pyuria and tuberculosis must be made with care. This latter condition presents many problems in its diagnosis and should ever be present in the mind of the examining physician.

In the treatment of amicrobic pyuria, the usual chemotherapeutic compounds that are so efficacious in combating the ordinary infections of the urinary tract are of little value. Local treatment gives only palliation, but the intravenous administration of arsenical compounds is almost specific. Along with this, however, I should like to make a plea for the appreciation of the part which foci of infection play in many of these cases. Permanent cure will frequently be impossible unless existing foci are eradicated and the teeth, tonsils, prostate gland, and uterine cervix are the most common.

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BIOLOGICAL DIFFERENTIATION OF
BENIGN AND MALIGNANT GROWTHS *

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ONE phase of an extensive constitutional study under progress in this laboratory has been an investigation of spontaneous neoplasia in the rabbit and, as a result of routine clinical and pathological examinations carried on over a period of years, a considerable series of tumors has been found. Cancers of the breast and of the uterus have occurred with the greatest frequency and have been subjected to more thorough study than the less common tumors of other organs. It is encouraging that in morphology, mode of development and biological characteristics, these growths bear a much closer resemblance to human cancers than do the corresponding tumors under study in other animal species.

A characteristic feature of the breast and uterine cancer is the occurrence of a well defined developmental history (Greene and Saxton 1938,¹ Greene 1939²). They do not arise as a sudden transition of normal cells but, on the other hand, represent the final step in a progressive developmental process during the course of which the primary neoplastic focus passes through successive stages of anaplastic cellular change, local tissue invasion, foreign tissue invasion and eventually metastasis. Transplantation experiments utilizing the anterior chamber of the eye as an inoculation site showed that the tumors could not be transferred to normal animals during stages of anaplastic cellular change or of local tissue invasion but could be transferred to normal animals during the stage of foreign tissue invasion (Greene 1940³). It was, therefore, concluded that anaplastic cellular change or local tissue invasion in the primary growths of these tumors did not constitute evidence of autonomy but rather stages in the development of autonomy, the final attainment of which was only evidenced by foreign tissue invasion.

In contrast to the failure of transfer to normal animals during

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stages prior to foreign tissue invasion, it was found that at such stages the developing tumors could be successfully transplanted to animals bearing spontaneous growths. This finding suggested that special factors were present in the spontaneous hosts but absent in normal animals and the nature of the endocrine changes constantly found in tumor bearing animals indicated that one of these factors might be an abnormal secretion of estrone. It was subsequently found that dependent tumors survived and grew in estrinized animals, whereas early death of the transplants occurred in normal animals used as controls and it was concluded that the constitutional status incident to an abnormal secretion of estrone was one of the factors essential to the continued growth and development of the tumors (Greene 1940⁴).

Cancers of the breast and uterus have been carried for many serial generations in normal rabbits and experimental investigations have been concerned with attempts to alter malignancy and to determine the immunological status of animals during different stages of tumor growth (Greene 1939,⁵ 1940³). The tumors have also been successfully transplanted to foreign species, including guinea pigs, hens, goats, sheep and hogs, by means of the anterior chamber technique (Greene 1941⁶). The tumors receive a blood supply from the alien host and grow progressively. The cells of the transplant, however, are descendants of the original tumor and not derivatives of the foreign species.

The anterior chamber has also been used for the heterologous transplantation of mouse tumors and it has been found that in this species tumors undergo the same biological phases of dependency and autonomy observed in the development of rabbit cancer.

It has also been possible to transplant human tumors to lower species using this route of inoculation (Greene 1942,⁷ 1944⁸). A considerable series of human tumors have been tested and it has been found that successful transplantation to normal animals could only be performed after the occurrence of foreign tissue invasion and it was concluded that, in human as in rabbit tumors, this stage marks the attainment of autonomy.

An interpretation of the significance of the capacity of cancer tissue to grow in alien hosts necessitated a more accurate definition of the limits of heterotransplantability and a series of experiments was instituted to determine whether or not this power was shared by other tissues. Benign tumors, normal adult tissue and normal embryonic tissue

(Greene 1943⁹) have been tested with respect to this property as well as to the ability to survive and grow in other environments and the results are presented in the accompanying chart.

TRANSFER

| <i>Tissue</i> | <i>Autologous</i> | <i>Homologous</i> | <i>Heterologous</i> |
|----------------------------|-------------------|-------------------|---------------------|
| Normal Adult | + | + | — |
| Normal Embryonic | + | + | + |
| Benign Tumor | + | — | — |
| Cancer | + | + | + |

The property of heterologous transplantability accents the relationship between cancer and embryonic tissue and suggests the possession of a common attribute that differentiates them biologically from other normal and pathological tissue states.

The primary conclusions indicated by the findings described in this abstract are first, that the rabbit cancers are not simply local tissue diseases but, on the other hand, represent local manifestations of a generalized constitutional disorder and, second, that in the rabbit the primary neoplastic focus is not a cancer and that before becoming a cancer it must undergo a process of progressive evolutionary development. Development to cancer will not take place in normal animals but is dependent on a special constitutional status which may be evoked experimentally by the administration of estrogenic substances. Both human and mouse cancers undergo a similar developmental course in their advance to cancer and in all of the species studied this course is characterized by dependent and autonomous phases.

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE



DECEMBER 1944

ADDRESS OF WELCOME *

ARTHUR FREEBORN CHACE

President, The New York Academy of Medicine

T

HE New York Academy of Medicine has chosen for its Seventeenth Annual Graduate Fortnight the enormously important subject: *Infectious Diseases and Their Treatment*.

We are in the midst of a period of world strife, and we are overwhelmed by the enormous destruction which it involves. Modern warfare is indeed devastating, but it seems appropriate to observe that in the history of mankind the infectious diseases have proven themselves to be even more destructive than the worst of wars. It is undeniable that all the destruction of all the wars that mankind has waged does not even remotely approximate the destructiveness of the infectious diseases. In witness, we need to recall but a few instances of pandemic and epidemic diseases: the Black Death, that destroyed more than a quarter of the population of the world, the great epidemics of typhus, cholera, typhoid and yellow fever, that have from time to time raged in Asia, Europe and in the Western Hemisphere. Think also of the great epidemics of cholera infantum which annually afflicted and destroyed countless thousands of young children. In this very time of universal strife and conflict it may be some slight bolster to our faith and hope to recognize that if we have not been able to curtail

* Delivered October 9, 1944 at the 17th Graduate Fortnight of The New York Academy of Medicine

the destructiveness of war, we have at least made great headway in our conquest of the even greater destroyer, the infectious diseases.

It is nigh on to a century since the first advance against the infectious diseases was made. The achievements of this short century of progress are marked by three major epochs. The first is represented by the monumental works of Pasteur, Koch, and Lister, and marks the recognition of the microbic causes of infectious diseases and their control by the methods which we collectively call "antiseptic." It is pertinent again, in the light of the World War to attest to the international character of the medical science by pointing out that the modern science of bacteriology and antisepsis was the product largely of a Frenchman, a German, and an Englishman.

The second epoch in the war on the infectious diseases marks the development of the vaccines and the immune sera, and here again we find among the great pioneers the Frenchman Pasteur, the German von Behring, the Englishman Wright, and the Japanese Kitasato.

The third epoch, and the one which promises to prove greater even than the two preceding, marks the achievement of a truly effective chemotherapy. The extraordinary growth and achievement of the chemical means for combating within the body of the host the microbic, and in some instances, the virus agents of disease, we have ourselves witnessed in the last few years. This last achievement is so vastly great, that we can appreciate it only by a deliberate account of its accomplishments.

Our chemotherapeutic agents, together with penicillin, have enabled us to gain much more than an even chance for survival in a number of diseases which heretofore were practically invariably fatal. To name but three instances, we can cite: pneumococcal meningitis, hemolytic streptococcal meningitis, and staphylococcal septicemia. Numerically more significant is the marked reduction in the mortality rates achieved through the use of chemotherapeutic agents in the more common and widespread diseases which heretofore carried with them a relatively high mortality rate. The classic example of this is, of course, the pneumonias.

No less significant, too, are what might be called the "unseen benefits of chemotherapy," namely their effectiveness in preventing complications—the secondary effects of injuries and diseases, which in time past frequently proved much more grievous than the initial disease or

condition. We see this not only in civil life, but more particularly today on our battle fields, where, through the use of the sulfanilamides and other compounds, those injured are spared serious infection. In civil life, an illustration is the rapid cure of gonorrhea and of early syphilis.

I have made reference to the short century of progress in our conquest of the infectious diseases, and have cited three epochs that characterize this achievement. There is a fourth one which needs to be noted, since it has a bearing on a new undertaking of the Academy. Medicine was not the only beneficiary of the great discoveries in bacteriology. Business and commerce also benefited enormously. Animal husbandry and food preservation are two instances. But then, significantly, business and industry have in turn become great benefactors of medicine, and this is notably the case in the fields of pharmacology, in the production of biologicals, and in the manufacture of the chemotherapeutic agents. The practice of modern medicine is inconceivable without scores of products made available to the practitioner through the industrial pharmaceutical organizations. The neighborhood druggist still plays a vital role in "filling the physician's prescription," but he fills it with products that have been made available to him by the pharmaceutical manufacturers. It is appropriate to recognize also that in recent years the pharmaceutical manufacturers have contributed substantially to research in the fields of therapy.

In recognition of the educational value of the research that is being done by these manufacturers, The New York Academy of Medicine has established a permanent exhibit of the newer remedial agents produced. It is the intent of the Academy to make available to the medical profession through this exhibit current information on the valid developments in chemotherapy, and in other forms of therapy.

As I have already said, the purpose of this year's Graduate Fortnight is devoted to the subject of "Infectious Diseases and their Treatment." On our program you will have the privilege of hearing the ablest scientists of our time.

In the name of The New York Academy of Medicine, I welcome you to one of our most thrilling Fortnights, for today Nature has released to us more and more of her secrets. Through this conference, as we look down the vista of the future of the art of healing, we realize that we have made substantial progress in the long march toward the greater fulfillment of our goal—the healing of the sick.

THROMBOPHLEBITIS — MEDICAL TREATMENT *

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IN THIS medical era of an ever increasing number of specific therapeutic measures many efforts to find such treatment for thrombophlebitis have so far failed to bring forth a cure. When one reads the literature on this subject he is struck by the numerous methods of treatment suggested by the many laboratory and clinical investigators. Ochsner and DeBakey¹ in their Shattuck Lecture delivered before the Massachusetts Medical Society in May of 1941 leave one bewildered by the conflicting suggestions offered by the numerous investigators reported by them, despite their own attempts to draw some semblance of therapeutic order out of the chaos. Three hundred and fifty-nine references are included in their bibliography.

In November of 1940 Irving S. Wright,² with whom I have been associated in the field of peripheral vascular disease, read a paper on thrombophlebitis in this auditorium. I was at that time in accord with the views he presented. My opinions to be expressed here tonight are at some variance with those in his paper. The past four years have seen a large amount of investigative work reported on this subject, both despite of and because of the war. Vascular disease has assumed more importance as a result of the peculiar circumstances of war and many of the reported observations can be applied to our subject.

I shall, therefore, attempt to evaluate the present medical therapy of thrombophlebitis, first from the impressions obtained from the literature of the last four years and secondly from our own experiences in clinical studies and laboratory investigative work; this latter information being impaired somewhat by a reduction in our investigative staff due to the war.

Wright in his paper reported that of the last 70,000 patients admitted to the New York Post-Graduate Hospital, 182 or 0.26 per cent

suffered from thrombophlebitis on admission or during their period of hospitalization. Since then there have been thirty-five thousand eight hundred and fifty-eight further admissions with 254 cases of thrombophlebitis or an incidence of 0.70 per cent. This increase in percentage is due to a larger number of cases of thrombophlebitis admitted from the Vascular Clinic, in which about 10 per cent of the cases suffer from thrombophlebitis. The average rate, therefore, for over 100,000 patients is 0.44 per cent. This low rate is probably due to the fact that no obstetrical cases are admitted to this hospital and perhaps, we hope, due to the better preoperative and postoperative care as a result of a very active vascular clinic.

Definition. When one uses the term thrombophlebitis he implies two processes. First a thrombosis and secondly an inflammation. It is theoretically possible to have simply a phlebitis without thrombosis and likewise a thrombosis without inflammation. However, such clear cut entities seldom if ever exist and, therefore, the term thrombophlebitis is justifiable in the majority of instances. In approaching this disease from the therapeutic standpoint it is becoming more and more apparent that one must decide which of these two factors predominates.

In the case of phlebothrombosis the irritative or infectious factor is usually minor and often not detectable while in an acute phlebitis the thrombotic factor may be unimportant with most of the process perivascular. In the first instance we find the so-called red clot or agglutination clot loosely attached to the vein wall with long portions unattached and in the second instance the white or inflammatory clot which is firmly attached to the wall often partially invading the various layers of the vein secondarily to the destructive process. As has often been said the primary thrombotic lesions predispose to embolic episodes while the inflammatory lesions are less apt to evidence such complications. However, let me emphasize that both processes are subject to this serious complication. The lowest incidence of emboli occurs in that condition known as phlebitis migrans; where the lesions are limited to the superficial veins, frequently of a small caliber, and in which the pathology is largely perivascular. As the lesions clear little or no permanent change in the vascular walls is evidenced from a clinical standpoint. However, in the past six months I have observed two patients suffering from migratory phlebitis with pulmonary embolism.

Although the subject of this paper is therapy one cannot approach

it intelligently unless he is able to distinguish the type of process active in each patient. While it is true that certain principles of treatment are indicated for both processes, the approach to one is basically medical and to the other surgical. In most of the literature there is a dearth of helpful information in differentiating these processes.

Individuals suffering from superficial phlebitic lesions usually manifest redness, swelling, increased heat, fever, leukocytosis and an increased sedimentation rate. Those with deep vein involvement may have cold, cyanotic extremities due to the secondary vasospasm of the arterial supply.

In primarily thrombotic lesions evidence of a tender cord-like formation along superficial veins or tenderness to deep pressure, or pain in the calf with forced dorsi-flexion of the ankle (Homan's sign) may be the only symptoms. Veal³ and DeBakey et al⁴ have shown the venogram to be an important diagnostic aid in demonstrating thrombotic lesions in the deep vessels.

Edema is of little value in differentiation as it depends on the location and degree of thrombosis as well as on the activity of the patient and other complicating factors, such as cardiac, thyroid and metabolic disorders.

Since all therapy should depend to a large extent on a knowledge of the factors which produce the disease, let us review our present state of information regarding the conditions that may cause or predispose to thrombophlebitis. Barker et al⁵⁻¹⁰ in a recent statistical review of cases have brought out many of these facts.

Age. It has been shown that in men thrombophlebitis occurs most frequently between the ages of 50 and 70 while in women between 40 and 60.

Weight. Individuals over 200 pounds in weight are several times more subject to thrombophlebitis than those under 200. Barker quotes an incidence of 4 per cent in patients under 200 pounds and 8 per cent in those over 200 pounds.

Sex. Females are more subject to thrombophlebitis than are males, with a ratio of three to two. Childbearing is probably the chief cause for this difference.

Occupation. Those subjected to work with long periods of standing are prone to develop varicose veins and, therefore, become subjects for thrombophlebitis. Occupations where trauma to the extremities

may frequently occur predispose to this disease. Certain occupations may cause diseases of the blood, such as methemoglobinemia, which reduce the nutrition to the vessel walls and precipitate arterial and venous disease.

Tobacco. It has been repeatedly shown that marked vasospasm with reduced blood flow results from smoking.^{11,12}

Surgery. From 1 to 2 per cent of surgical procedures have been reported as complicated by thrombophlebitis.

Disease. By and far the greatest number of cases of thrombophlebitis are associated with or secondary to primary disease. The chief conditions encountered are:

1. Cardiac disorders with impaired blood flow to the extremities.
2. Infection with secondary vein involvement associated with sluggish peripheral blood flow.
3. Varicose veins with blood stagnation.
4. Fungus infections as portals of entrance for infection.
5. Blood dyscrasias, especially polycythemia vera, and severe anemia.
6. Conditions affecting the clotting mechanism of the blood especially those in which the prothrombin time is decreased. Such conditions may be due to many causes such as alterations in mineral balance, the .K factor, thrombokinese, etc.
7. Cancer with obstruction of venous return or by general debility of the patient with reduction of blood flow.
8. Dehydration with hemoconcentration.
9. Chilling with its associated vasospastic phenomena.

THERAPY

During the last four years it seems to me that therapy has tended to become more radical. Wright² in his 1940 paper states "Conservative therapy is usually adequate." I still believe that simple measures directed at all the factors present in each individual case will usually have the greatest measure of success without exposing the patient to the ordeal and possible complications of more radical approaches. However, I am convinced that ligation of veins to prevent embolism, repeated paravertebral sympathetic nerve blocks and embolectomy will in selected cases not only reduce mortality or prevent embolism but will shorten the course of what is too often a long protracted disease.

PROPHYLACTIC THERAPY

The therapy of thrombophlebitis is most important from the prophylactic standpoint. The prophylaxis of the infections and contagious disease is well established with modern sanitation, sera and vaccines. However, when we realize that 1 to 2 per cent of surgery and serious injury is complicated by thrombophlebitis we are faced with the fact that probably 50,000 to 100,000 cases of this condition might be prevented annually in this country by more careful management of the patient. This holds particularly if the patient is past middle life or overweight. Therefore, any patient subjected to surgery or trauma should be treated to prevent this serious complication.

Prophylaxis starts with a careful evaluation of the individual. Various authors ^{13,14} report from 30 to 90 per cent of all patients developing thrombophlebitis have some form of heart disease. This observation is important from two angles. First with impaired cardiac function, especially with right ventricular failure of any degree, reduced flow to the extremities leads to venous stasis and predisposes the patient to thrombosis. Secondly in patients of the 50 year and older age group heart disease is usually on the arteriosclerotic basis and this is frequently associated with peripheral arteriosclerosis further reducing blood flow to the extremities. It, therefore, is important to treat the heart by whatever means indicated to effect its maximum output and to employ all means available to overcome any coexisting vascular spasm in the extremities. It has been our experience, working in a hospital with an active cardiac and an active peripheral vascular clinic keeping the surgeons vascular conscious, to see a low incidence of postoperative phlebitis. I believe the main reason for this is the close coöperation between the surgeon and the vascular specialist. Not only must the preoperative care of a cardiac be such as to have the cardiac function as nearly normal as possible but postoperative medication must be administered to maintain this level of efficiency. Too often we see large volumes of fluid poured into a circulatory system too rapidly and unnecessarily. In addition to overloading the heart one occasionally sees enough sodium citrate used in banked and fresh blood put into the system to upset the mineral balance of the body leading to heart failure and sluggish peripheral circulation and occasionally death.

From the standpoint of the peripheral circulation let us first con-

sider arterial supply. In both the normal and diseased states vasospasm plays a tremendous role in reducing blood flow. The emotional stress of even minor surgery, of worry unassociated with illness, pain associated with the surgical procedures may reflexly lead to reduced blood flow due to spasm. Tobacco nearly always increases this spasm and certainly in any case where thrombophlebitis might be suspected of occurring it should be eliminated pre- and postoperatively. Certain forms of medication such as ergot increase vascular spasm and all vasospastic medication should be avoided if at all possible. One wonders whether the frequent use of ergot in obstetrical cases is not one of the reasons for the greater incidence of thrombophlebitis in these patients. Warmth to the extremities in the form of woolen leggings or better a heat cradle with a temperature regulated to 94°F. will promote vasodilatation. Ochsner and DeBakey¹ have reported a marked reduction in thrombophlebitis by the application of the heat cradle postoperatively. Excessive temperatures are to be avoided because of the danger of causing a burn in tissues whose blood supply may be inadequate to meet the increased metabolism caused by the excessive heat.

The second problem to be considered from the general standpoint is the question of obesity. This abnormality contributes to possible thrombophlebitis in several ways. It may cause the patient to be very sedentary with resulting poor peripheral musculature and it is frequently associated with varicose veins.

It has been our routine policy to reduce overweight patients before doing any surgery except that which is emergency. In the latter instance every method known to promote more efficient peripheral blood flow must be applied pre- and postoperatively.

Thirdly, hypothyroidism plays at least a dual role in predisposing to thrombophlebitis. Lange¹⁵ has shown that the circulation time in this condition as measured with Fluoresce intravenously and its rate of flow observed by ultraviolet or so-called "black light" is markedly reduced. This is in agreement with many observations previously reported.¹⁶ In addition patients manifesting lower metabolic rates have distinct disturbances in tissue nutrition which may be a factor in causing alterations in the tissues of the vessels themselves. In view of this finding many surgeons have routinely employed thyroid extract at operation as a prophylactic against thrombophlebitis and the reports

of its efficacy vary greatly. It might be better to limit its use to those individuals whose basal metabolic rate is found to be low and whose peripheral circulation time is slower than normal.

Blood dyscrasias are usually recognized since a complete blood count is nearly a routine in every medical and surgical problem. Perhaps polycythemia vera is the hematological condition most frequently responsible for thrombosis. Although intravascular clotting is usually found in the smaller arterial radicals it not infrequently involves the venous system. The anemias may also cause venous pathology and are most likely to when marked. This theoretically might occur as a result of poor nutrition to the vascular wall and to reduced venous flow secondary to systemic muscular weakness and to inanition. The diseases of the white blood cells are most apt to produce venous thrombosis by secondary back pressure due to enlarged lymphatic glands, splenomegaly or hepatomegaly. Treatment of many of these dyscrasias is often impossible or at best inefficient.

Cancer by pressure, or by invasion of the veins themselves, is a common cause of thrombosis and frequently the first evidence of such a process is embolism. I have seen one such case in which fatal embolism occurred in an apparently healthy individual without complaints and only at postmortem was there found a pelvic malignancy invading the right iliac vein. It, therefore, behooves us in recognized cases of malignancy to treat enlarged glands with x-ray or radium and to do everything possible to increase blood flow to avoid the annoying complication of a phlebitis.

In any patient with a major infection such as typhoid fever, pneumonia, colitis, etc. secondary thrombophlebitis is all too common. Aside from the elimination of the infection, prophylactic measures against vein involvement must consist in maintaining a fair degree of bed activity if possible, maintaining adequate hydration, efficient cardiac output and replacement of blood by transfusion or iron therapy. Minor infections, especially those in the lower extremities including fungus lesions are a common point of origin of thrombophlebitis. Thompson¹⁷ has done extensive work on the relationship of the fungus infections to vascular disease. It is our observation that such lesions are in some way definitely responsible for the development of thrombophlebitis despite the negative result reported in culture studies by Dunham,¹⁸ one of our former fellows.

Smith and Allen¹⁹ of the Mayo Clinic have shown a marked reduction in blood flow (venous return) in the extremities from chilling. They have reported a slowing of up to 67 seconds from the lower extremities as compared to a normal of 22 seconds. Since there is rather clear cut evidence that reduced flow through the veins predisposes to thrombosis every bed ridden case, medical and surgical should be guarded against chilling. This is particularly true in all surgical cases, especially in the immediate postoperative hours.

A controversial point in the postoperative care of the surgical patient as well as of the chronic medical patient concerns the position of the extremities in relation to the heart. The majority of clinicians feel that elevation of the lower extremities above heart level promotes more rapid venous return. However, Frykholm and Patey²⁰ claim that elevation of the head of the bed causes the veins to be well filled with blood, avoids contact of the intimal surfaces and possible pressure trauma and necessitates leg movements to maintain this position in bed, which in turn tend to cause a better blood flow due to constant muscular activity.

With the modern Gatch type of hospital bed many positions can be made readily available. However, one which is frequently used has certain serious drawbacks from the standpoint of thrombophlebitis. The patient in a Fowler's position is probably subjected to three hazards. First, pressure in the popliteal space and kinking of the vessels there, leading to reduced arterial inflow and obstruction and delayed venous return. Secondly, the pelvis becomes the low point with possible stagnation of blood in the veins in this location. Third, pressure on the deep veins in the calf as the lower leg hangs in a dependent position with the calf resting heavily on the mattress.

It is my opinion that the correct position for the lower extremities can be best determined by several simple observations which would indicate maximum flow with the least degree of stagnation, e.g.:

1. Elevation of the foot of the bed to a slight degree only so that the veins over the dorsum of the foot barely collapse but not high enough to cause a complete flattening of the veins or especially a pallor of the skin. This latter point is extremely important if the patient is suffering from a complicating obstructive arterial disease.

2. Higher elevation in patients with good arterial supply but with varicose veins or old phlebitic scars.

3. Slight depression of the foot of the bed by elevation of the head in individuals with markedly impaired arterial supply. The degree of depression can be regulated by noting the color of the skin and the position selected should be one which prevents excessive rubor or cyanosis.

4. The ideal position should likewise prevent the development of edema or help to reduce it if present from systemic disease such as cardiac failure.

5. The head of a Gatch bed may frequently be somewhat elevated to aid in better cardiac function and in reducing pressure on the femoral vein, as demonstrated by Friedländer.²¹

6. In patients in whom the development of thrombophlebitis is likely, the oscillating bed of Saunders²² simplifies this problem of the position of the extremities. By constantly altering elevation and depression it promotes good vascular function.

In concluding my remarks on the position of the extremities let me emphasize one point. It is seldom necessary to go to extremes in finding the optimum position of the legs, only slight changes from the horizontal position are usually indicated.

I need spend but a few moments on the question of mobilization. There is practically universal agreement on the need for muscular activity in postoperative patients, chronically ill individuals and in even healthy patients. The "shelter legs" of this war are typical examples of poor vascular return. These individuals keep their legs in the dependent position with little motion for long periods. The venous return is further impaired by hard chairs and sharp edges. Within the past month I have seen a case of leg edema with a small localized thrombotic lesion in a thin young girl who typed for nearly 12 hours steadily, sitting on a chair which was too low and to which she had added several telephone books.

I believe one of the greatest mistakes is to make the ill patient too comfortable. A soft mattress with the bed in an exaggerated Fowler's position, the use of sedatives and the fear of moving about often predispose to venous stagnation. A hard bed, a nurse who sees that the patient moves frequently, are of great help. The oscillating bed in addition to obtaining the effects of gravity also causes the patient to move about. Many surgeons have shortened their postoperative bed rest to a few days instead of weeks. In addition they have advocated,

as does de Takats²³ active bed exercises. Campeanu,²⁴ Zava²⁵ and von Jaschke²⁶ have reported in several thousand operated cases which had a radical degree of early ambulation a very marked reduction in thrombophlebitis. In one series of 6000 operations there was no case of embolism.

Still another prophylactic measure of importance is the need for full respiratory excursions which act as an aid to force venous return from the extremities. Avoidance of deep anesthesia, heavy doses or prolonged use of narcotics, the use of CO₂ as a respiratory stimulant are all methods very well known but *all too frequently* overlooked.

Elastic supports in the form of Ace bandages, rubber bandages or elastic stockings will prevent stagnation of venous blood in patients with varicose veins and will, therefore, permit a lower position of the legs in bed and mobilization of the patient for longer periods.

We have at hand today in addition to the prophylactic measures already discussed new agents of great value in the prevention of this dread complication of surgery and illness. They are basically, first the new compounds being used so effectively to combat infection, such as the sulfa drugs and penicillin and its related substances and, secondly, the anticoagulants, especially heparin and dicoumarol. Figures are not available as to the reduction of thrombophlebitis and embolism as a result of the use of the first agents. Certainly the reduction in days of bed care alone as a result of the prevention or cure of infection by their use would naturally reduce venous pathology. It is highly possible that they specifically shorten the course of and perhaps cure certain types of thrombophlebitis.

The anticoagulants have been shown to practically eliminate this complication of surgery. Murray²⁷ has shown in 750 surgical cases treated with heparin no cases of thrombophlebitis. However, these new therapeutic agents are either expensive, hard to administer or have serious complicating reactions that render their universal use at present unwise and in many instances impossible except in large hospitals with efficient laboratory assistance.

Our next step, therefore, is to spend some time on the question of the diagnostic aids available which would help us decide in which patients thrombophlebitis may occur and in whom prophylactic measures are indicated including possible radical medical treatment or surgical intervention.

From the *Clinical* standpoint the following observations would point to a possible impending thrombophlebitis.

1. A history of a previous thrombophlebitis, either postoperatively, postpartum or spontaneous.

2. Any of the general physical defects or diseases already discussed such as obesity, cardiac disease, blood dyscrasias, etc.

3. An increasing pulse rate, the cause of which is not evident.

4. A slight degree of fever, the cause of which is not evident.

5. A general uneasiness or awareness of impending trouble in a patient who otherwise has been doing well clinically. This is a frequent observation but often overlooked.

6. Vague discomfort in an extremity.

7. Slight edema in one extremity.

8. Coldness or clamminess in one extremity.

9. An unexplained chill.

10. Evidence of dehydration.

Such observations as well as the tests to be described should be most intensively made from the 5 day to the 15 day postoperatively. Barker²⁸ et al have shown that embolism occurs most frequently during this period.

From the *Laboratory* standpoint:

1. The erythrocytic sedimentation rate can be of real value but frequently remains normal in severe forms of thrombophlebitis. However, an elevated rate when no other cause for it is present or a daily rise in the rate would point to possible vein involvement.

2. A complete blood count should be made daily in each case suspected of developing thrombophlebitis. Elevation of the leukocytes is usually present after the pathology is clear cut but slight daily increases, with a relative increase in the polymorphonuclear leukocytes is likewise of some significance.

3. A hematocrit reading will evidence a hemoconcentration.

4. Since Wright's paper in 1940, considerable interest in prothrombin time studies has developed. The usual methods of studying the coagulation of the blood had been of little value from the diagnostic standpoint in thrombophlebitis. Blood clotting, bleeding and clot retraction times varied only slightly from normal in even severe cases of this disease. However, the increased activity or amount of prothrombin present in cases of thrombophlebitis can readily be measured by

methods such as described by Quick,²⁹ Shapiro³⁰ and others. This relatively new test unfortunately is affected by several variants and there are several methods used by laboratories in general. Each investigator has his own variations of technique. For instance various workers use different thromboplastic agents, such as brain tissue, lung tissue and viper venom, each substance giving a somewhat different normal standard rate. Temperature variations may affect the end point. Shapiro³¹ has recently published a method in which he attempts to overcome these difficulties and in his laboratories he has found the normal prothrombin time to be 15.5 seconds with a standard deviation of plus-minus 1.5. He likewise feels that the use of diluted blood serum gives a more sensitive test since in dilution "the naturally occurring anticoagulants are made ineffective when diluted 1:8, while at the same time the contained prothrombin retains adequate activity to induce clotting." This he has shown by demonstrating a drop in the prothrombin time using diluted serum without significant change in the test with undiluted serum. He has also observed the reverse in which the whole serum gives a prolonged prothrombin time and the dilute a normal time. This would indicate the presence of an anticoagulant type of substance in the serum. This effect is lost on dilution. His standard for the dilute test is 39.5 seconds with a deviation of plus-minus 2.5. The importance of this double test as a diagnostic aid in suspected thrombophlebitis is shown by a reduction in prothrombin time in the dilute serum test with little or no change in the prothrombin time with the use of concentrated serum.

It has been shown that in thrombophlebitis there is frequently an increased prothrombin activity which may possibly occur either before thrombosis actually develops or at the very onset of the disease. Therefore, a test which will indicate such a change in prothrombin is of utmost value. I hope that we rapidly develop a uniform simplified standard test of this type and that the preliminary reports are confirmed. Our experience with dilute and concentrate prothrombin time studies tend to confirm Shapiro's observations.

THErapy

The treatment of thrombophlebitis resolves itself as in many fields of medicine, into two main divisions, surgical and medical, with the two frequently used together. I have attempted to differentiate the

types of thrombophlebitis and have discussed diagnostic aides. Some type of surgery is indicated in those patients suffering from lesions in which embolism is likely, in those with an accompanying high degree of arteriolar spasm and in suppurative thrombophlebitis.

The principles underlying the medical treatment are as follows:

1. Removal of the cause if one is known.
2. Increase of blood flow in the involved area.
3. Reduction in the ability of the blood to coagulate.
4. Prevention of embolism.
5. Prevention of edema.

Since the possible causes of thrombophlebitis are many there is a relatively small percentage of the cases in which a cause may be removed. Localized infections on extremities, infected varicose ulcers, fungus infections of the feet and legs, systemic or focal infections on the body, should be treated medically or surgically as indicated. With the discovery of the sulfa drugs and penicillin, infections are more easily eliminated. In those cases of thrombophlebitis where no primary disease can be found or where its removal is impossible or must be delayed, these two types of drug therapy may be used in an attempt to destroy a possible etiological factor of the thrombophlebitis.

Our success with the sulfa drugs has been only fairly satisfactory and at best their efficiency is difficult to determine. Acute cases with febrile reaction, high sedimentation rate and leukocytosis frequently make excellent spontaneous recovery and any form of therapy is hard to evaluate. However, it is my opinion that the use of one gram of sulfadiazine with adequate alkalization given every four hours does shorten the course of acute phlebitis and may prevent the serious complication of suppuration. We have frequently observed a rapid fall in the sedimentation rate with patients on such therapy. Certainly the dangers from the serious acute forms of thrombophlebitis are far greater than from such a drug. Its use in the thrombotic forms is of course valueless except prophylactically and in the migrans or chronic forms it has proven of little value.

Penicillin, because of restricted use, has to the best of my knowledge had a limited trial in the therapy of thrombophlebitis. I know of only two cases in which it has been tried, one acute and involving the small vessels of the foot and which progressed rapidly during its administration. The other was a subacute thrombophlebitis of the saphenous sys-

tem in a patient with varicose veins and manifesting no improvement with penicillin. Moreover, in both instances other conservative therapy was utilized. As more of this product becomes available its effect should be studied in thrombophlebitis.

Fungus infections either primary or secondary which are commonly found in a majority of patients suffering from thrombophlebitis of the lower extremities must be eliminated before venous pathology will permanently clear. Thompson¹⁷ has recently published an arbeit on this subject and I refer you to his paper for a most complete summary. Although many investigators do not feel as definitely as he does as to the relationship of the various fungus organisms and vascular disease no one can dispute their frequent association. Since the tissues of the extremities infected with fungus and suffering from impaired venous drainage due to thrombophlebitis are easily damaged by necrotizing agents a non-irritating but efficient fungicide must be used. Also since the fungus is frequently active under thickened eschars or dry scaly skin this agent must be used in the form of warm soaks or compresses which will soften these insulating layers of dead material. A solution of potassium permanganate of 1:4000 or 1:8000 has produced the best results in our clinic. Where dependency is unwise, moist compresses of this solution kept warm in a heat cradle set for about 90°F. have proven very efficient.

Vasospasm is frequently an associated finding in thrombophlebitis. It tends to reduce blood supply, thereby permitting infection to spread and thrombosis to extend. All methods available should be utilized to increase arterial supply and increase venous return. Paravertebral nerve block offers real aid in this problem. However, conservative measures frequently can accomplish much. Heat has, therefore, become a greater therapeutic aid than cold. Warm moist packs over an extremity in which there is superficial phlebitis give quicker relief of pain, reduction of redness and swelling and temperature than do the cold or ice packs used for so many years. Reflex heat in the form of warm blankets, hot water bottles or electric pads applied to the upper part of the body will usually produce vasodilatation. Excessive cradle heats over the involved extremity are to be avoided as vasospasm may result and increased metabolism of tissues with sluggish blood flow may cause tissue breakdown with increased pain and ulceration.

What has been said about the position of the extremities under pro-

phylactic treatment holds true in the treatment of acute thrombophlebitis. Any position in which cyanosis or rubor are increased or edema aggravated is to be seriously avoided.

There are those, such as Edwards³² and Meyer,³³ who advocate active mobilization in the form of walking of the involved extremities, together with supporting bandages to prevent stasis and edema. They report no increase in embolization and a more rapid healing. However, I am sure that in the primarily thrombotic lesions and in the actively acute phlebitic lesions the majority of clinicians favor much more conservative therapy in the form of bed rest with or without surgery.

Drugs play a minor role in the therapy of this disease. Pain relieving drugs and hypnotics should be prescribed carefully since complete mobilization resulting from their use may predispose to further thrombosis. Vasodilating drugs are relatively inefficient although papavarine in doses of one grain or larger as advocated by Katz³⁴ at four hour intervals appears to have real value. Whiskey and aspirin often seem to produce almost the same effect. Murphy³⁵ reported improvement with the use of Mecholyl (acetyl-beta methyl-choline chloride) by iontophoresis. The administration of this drug in this manner produces definite vasodilatation as shown by reports from Kovacs³⁶ of our Clinic and should be of value.

Much investigative work is now under way as to the effects of various drugs on the coagulability of the blood, especially on the prothrombin time. Aspirin has been shown to act as an anticoagulant by Link³⁷ and digitalis as a coagulant by Macht.³⁸ These findings if verified should have some bearing on the use of these drugs in thrombophlebitis.

Before leaving the question of increasing blood flow one should emphasize the need of *eliminating tobacco completely* from the habits of one suffering from thrombophlebitis. It is one of the most marked vasospastic agents widely used. Ergot in any form including ergotamine tartrate is likewise contraindicated. It is my opinion that the majority of patients suffering from phlebitis migrans will not remain free of attacks as long as they continue to smoke and I have seen during the past year 10 individuals with this disease suffer recurrences very shortly after the resumption of smoking.

Blood viscosity can be reduced by injections of tetrathione as recommended by Theis. In patients with associated increased hematocrit

readings or mild secondary polycythemia this agent is indicated.

In thrombophlebitis an increased tendency of the blood to coagulate must be counteracted if possible. Hyperprothrombinemia can be counteracted by the use of anticoagulants. I refer you to the paper of Prandoni and Wright given before the Academy in 1942 as well as to numerous articles on these substances.^{7, 10, 11, 12} There is little evidence to indicate that either heparin or dicoumarol will resolve a thrombosis but both of these substances will prevent to a great degree the formation or progression of thrombi and are, therefore, of real value in the medical treatment or in conjunction with the surgical treatment of thrombophlebitis. In any case showing evidence of embolization their use is indicated whether the treatment is limited to medical therapy or is combined with vein ligation or paravertebral nerve block. In the acute case heparin is indicated as its action is almost immediate and its serious effects can be eliminated by cessation of the drug. It is expensive, difficult to administer by the necessary continuous intravenous route and hard on the morale of the patient. Dicoumarol is easily administered by mouth (or vein) but requires 48 hours to produce its effect on prothrombin activity and has a long drawn out effect lasting days. Any serious side effect must be counteracted by the transfusion of whole fresh blood still maintaining thrombokinase or by large doses of Vitamin K. Litchfield¹³ has shown that 64 mgm. of menadione bisulfite (hyknone) will stop hemorrhage from excessive dicoumerol.

The ideal application of these agents in acute thrombophlebitis is to start the therapy with both drugs and after 48 hours to discontinue the heparin. Heparin should be given in average doses of 35 to 40 mgm. per hour increasing or decreasing the dose to maintain a clotting time of between 20 and 30 minutes. This latter test must be done at least every four hours during heparin administration and oftener if the dose is altered. Three hundred milligrams of dicoumarol can be given with the onset of heparin therapy with 100 mgm. per day thereafter. Prothrombin rates should be determined daily after heparin is discontinued and the daily dose of 100 mgm. discontinued when the prothrombin rate increases above 40 seconds or doubled if it decreases toward normal. Anticoagulant therapy should be continued as long as active lesions persist and until one feels that all danger of pulmonary emboli has ceased if the prothrombin time remains within safely controlled limits. Prothrombin times must be taken daily for at least 10 days after

dicoumarol has been discontinued.

The dangers from these drugs are real and are mostly due to bleeding. Shlevin and Lederer⁴⁴ reported two months ago a case in which dicoumarol was administered because of retinal thrombosis but its effect was not followed by prothrombin time tests, the patient dying from cerebral hemorrhage. Like many another drug in medicine, improper dosage or its use in patients suffering from liver or kidney disease may result in serious or fatal outcome. Digitalis, an invaluable aid in cardiac disease, has certainly produced some deaths from improper prescription.

The prevention of embolism is one of the primary problems in the treatment of thrombophlebitis. The medical care as outlined, especially with the use of anticoagulants will go a long way in preventing this serious complication. However, surgery offers much and as I said once before tonight I have changed my opinion in the last four years as to its use. Dr. de Takats, who is much better qualified than I, will cover this part of the subject tonight. What is more important is the recognition of mild embolism and the institution of active therapy; medical, surgical, or combined; against further episodes. Any sudden increase in pulse rate or respiration, with or without cough or fever or pain in the chest should make one suspect pulmonary embolism. Its confusion with coronary thrombosis is common and the electrocardiogram is not always helpful in differential diagnosis. Even x-ray may leave one in doubt where emboli are small. Where the diagnosis is in doubt or the site of the origin of the emboli indefinite anticoagulant therapy is perhaps a wiser course than vein ligation.

The prevention of edema in thrombophlebitis is of two fold importance. First, edema means stasis and this may be the ground work for further extension of the process. Secondly, the prophylaxis of chronic lymphedema is the elimination of the process causing it as rapidly as possible. Therefore, when at rest sufficient elevation must be used to prevent swelling and with the resumption of activity swelling must be prevented by adequate support just as long as there is an indication of it occurring. Individuals should be removed from occupations or habits in which static dependency is present for long periods of time.

SUMMARY

A survey of the literature has been presented together with im-

pressions obtained from our own experiences with this baffling disease. I believe we have seen a tendency to resort to more surgical treatment in thrombophlebitis during the past four years, but as in all medicine the proper evaluation of the disease process will indicate the therapeutic approach, whether it be medical or surgical or, as in many cases, a combination of the two. I sincerely hope that the future will see most vascular problems such as thrombophlebitis handled by close coöperation between the internist and the surgeon.

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THE SURGICAL TREATMENT OF THROMBO-EMBOLISM AND ITS SEQUELAE *

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INTRODUCTION

The surgical treatment of thrombo-embolism must rest on the recognition of factors leading to thrombi and their propagation. The surgeon who ignores the fact that clotting of blood occurs because of slowing of venous return, intimal injury and increase in the clotting activity of the blood will simply use mechanical measures to inhibit the spreading of thrombosis. This would be very much like operating on a diabetic without the benefit of controlling his carbohydrate and fat metabolism. Surgical measures then constitute simply one phase of our therapeutic measures, which have just been so thoroughly discussed by Dr. Duryee. A combination of all such measures is highly desirable and requires an intimate teamwork of surgical and medical departments.

The literature on this fascinating subject is vast and has been reviewed annually for the last ten years by Scupham and myself in the Archives of Internal Medicine.¹ For this reason I shall limit this discussion to the experience of our group. Many of the problems encountered are still unsettled and such a symposium as this helps to clarify controversial points.

FACTORS LEADING TO THROMBOSIS

Slowing of venous return. The surgeon is frequently confronted with patients whose venous return is retarded because they are put to bed, or because the operative procedure itself has diminished venous back-flow.² This can be conveniently measured by the ankle-to-tongue circulation time with decholin. In past years we have advocated the postoperative use of a stationary bicycle attached to the foot of the bed

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but have abandoned its use, since it is cumbersome and can not be used on a wide enough scale. Much simpler is the routine elevation of the foot of the bed on eight-inch shock blocks³ which measurably accelerates circulation time and takes no additional nursing care. In addition it straightens out certain acute angles and compressions of the venous return, which the customary postoperative position produces. The patients are asked to move about freely in bed (barring certain obvious exceptions) and are allowed to get out of bed reasonably early. By this I mean that no extremes are used. They are neither forced to get out of bed the day after the operation, nor are they made to lie absolutely quiet for fourteen days after a herniorrhaphy. Generally speaking they should have enough sedatives for the first forty-eight hours so that they move about in bed freely and are encouraged to do deep breathing exercises, such as Dr. Eugene Pool of this city prescribed many years ago.⁴ Then they are allowed to get up on the fourth or fifth day so that when the stitches are ready to be removed, they are ready to go home. With the use of non-absorbable suture material, such as silk and cotton, the hernias heal just as firmly if you let them get up the fifth as if you mobilize them the fourteenth day.

One of the most tragic types of death is that of the young man who has a herniorrhaphy and after a perfectly smooth convalescence, with no elevation of pulse and temperature, no indication of any peripheral venous thrombosis, drops dead on getting out of bed on the fourteenth day. It is difficult to escape the conclusion that a potent factor in such a patient's death is the prolonged immobilization.

Injury to the intima. The contusion, stretch or rupture of a vein obviously produces thrombosis, and these factors may later be responsible for the development of superficial varicosities. I wish to point to the not infrequent ankle edemas and tortuous perimalleolar varicosities which follow a simple sprain. Injuries to the knee-joint or to the patella, followed by rigid splinting are apt to be accompanied by a thrombosis of the popliteal vein, a result probably of injury and immobility. But injury does not have to be mechanical. Burns, frostbites notoriously produce thrombi. Certain infections, notably the pneumococcus and virus pneumonia, malaria, bacterial endocarditis, are known to be followed by thrombosis and at least part of the mechanism responsible for this is an intimal reaction, although the changes in the clotting factors are equally important. Infections, toxins may injure the intima, but by

far the most neglected phase of this problem is the allergic response of the vascular bed so clearly established for periarteritis nodosa⁷ and for streptococcus infections treated with sulfanilamides.⁶ For many years our group has treated Buerger's disease on the assumption that small increasing doses of typhoid vaccine desensitize the vascular bed to an unknown allergen.⁷ The work on nicotine⁸ and on ringworm infections^{9, 10} would suggest that these are specific sensitizing factors; there are probably others.

The surgeon's interest in such vascular allergies is explained by the fact that he may have to operate in the presence of such hypersensitivity and thus precipitate a thrombosis. The situation is especially obvious in Buerger's disease, in which a minor amputation or a sympathectomy may be the starting point of widespread thromboses in which venous and lymphatic reactions may play a part. That sensitization phenomena directly affect the clotting mechanism is to be discussed presently. Certainly our best indication of such hyperactivity to date lies in changes in the tendency to thrombosis to be described presently.

Changes in the clotting mechanism. Determinations of coagulation and bleeding time are used routinely to pick out patients who suffer from hemophilia, thrombopenia, purpura and other blood dyscrasias. But with the exception of Bancroft's clotting index,¹¹ no attempts have been made in the past to detect "clotters" among surgical patients who might be more apt to develop postoperative, postpartum or postinfectious thromboses. Attention should be drawn to the significance of prothrombin determinations on dilute plasma,¹² to the increased heparin resistance as measured in vitro¹³ and to the heparin tolerance of the patient. Since my experience is limited to this test, a brief discussion of its significance will follow.

It seems that each patient reacts individually to a certain standard dose of heparin. We chose one cubic centimeter (10 milligrams) of undiluted heparin given intravenously, and studied its effect on capillary coagulation time. The response to heparin depends on many factors some of which have been recently studied.¹⁴ (Table I.) One measures the excess of clotting factors, thrombokinase and prothrombin by their anti-heparin action; any condition which liberates thrombokinase, such as trauma to muscle, platelet destruction, or tissue necrosis, will flatten the tolerance curve; conversely, any method which throttles the production or liberation of prothrombin such as hepatic damage, constrict-

TABLE I

FACTORS INFLUENCING THE RESPONSE TO HEPARIN

| <i>Decreased sensitivity</i> | <i>Increased sensitivity</i> |
|--------------------------------------|--|
| Postoperative state ¹ | Sulfur compounds (sodium tetrathionate, sodium thiosulfate, sulfanilamides?) |
| Acute thrombosis ² | Prostigmine (or other parasympathetic stimulants) |
| Buerger's disease (acute phase) | Dicoumarol ³ |
| Polycythemia | Digitalis (small doses) |
| Severe burn, sudden dehydration | Hepatic damage |
| Acute hemorrhage | |
| Severe trauma | |
| Adrenal stimulation (anxiety? fear?) | |
| Digitalis (toxic doses) | |
| Carcinomatosis | |

¹ 3 to 4 days after a major operation.

² In any part of the vascular tree.

³ Walker, J. and Rhoads, J. E. *Surgery*, 1944, 15:859.

Unless otherwise stated, the observations are our own.

tion of hepatic veins (prostigmine) or which actually increases the heparin activity of the blood, such as the sulfur compounds, or raises the level of the heparin activator (albumin X of Quick¹⁵) will raise the tolerance curve. But most importantly there are people who perhaps at certain times or possibly consistently are hyporeactive to heparin, whereas others, a considerable number in our series (10 per cent) are hyperreactive and show symptoms of drug allergy when given heparin.

The significance of both of these groups existing in the adult surgical population is obvious. Could it be that the hyporeactors are the ones that need intensive prophylactic anticoagulant therapy, because the incidence of postoperative thrombosis is higher in this group? Such a study is now under way, but will require a rather large number of patients before it can be statistically significant. The hyperreactors are important, too, since the use of heparin in them is fraught with real danger. The bronchial spasm, the flushed face, the severe girdle or lumbar pain are mostly found in individuals who may have other

allergies. Some of these patients have never had heparin before but it must be remembered that the purest heparin contains 2 per cent nitrogen.¹⁶

Our present practice is to determine the heparin tolerance of every patient who is to receive heparin, since this helps in outlining the intervals between intermittent administration and also eliminates the hypersensitive individual. The prophylactic use of anticoagulants is limited to patients who have had previous thromboses, who have Buerger's disease, who have arterial or venous sutures. The treatment of thromboses by anticoagulant therapy has already been extensively discussed by Dr. Duryee.

Types of thrombosis. In his lectures on pathology Aschoff¹⁷ distinguished between a bland thrombus due to stasis and an infectious thrombus. Great credit is due to Ochsner and DeBakey for emphasizing and popularizing these two types and coining the descriptive labels of phlebothrombosis and thrombophlebitis.¹⁸ In a recent publication, Fowler and I¹⁹ made the point that every thrombosis may contain elements of both of these types but in different proportions. Thus for instance a thrombosis in the calf muscles of the leg, which starts as a bland, quiet type,²⁰ and has embolizing quality, becomes an infectious thrombophlebitis if it ascends to the groin and encounters a latent lymphadenitis and perilymphangitis, which so often exists at the root of the limb. Then the region becomes hot, tender, a high white count and elevated temperature may appear, and the clinical picture is that of an acute iliofemoral thrombophlebitis accompanied by vasospasm since it involves the adventitial and perivenous sympathetics. It has seemed to me that with the exception of the rather rare suppurative thrombophlebitis which often produces a bacteremia and metastasizing abscesses, most thrombi are phlebitic or not depending on the existence or degree of a latent infection in the wall or the perivenous lymphatics of the vessel. Thus a thrombus produced by injecting a sclerosing solution into a varicose vein will be a bland, non-inflammatory thrombus or a markedly inflamed, red, hard cord of thrombophlebitis depending on the extent of a "resting" infection in the injected vein.²¹ It seems as if this infection slumbers in the perivenous lymphatics since such a flare-up is often seen in patients who have infected ulcerations or ringworm infections in the periphery. As I have pointed out elsewhere²¹ the simple, mild trauma of a venipuncture may activate

such a thrombophlebitis. It is reasonable to assume, then, that the primary source of clotting is the bland thrombus due to the process of intravascular clotting and that the infectious quality is rendered by the segmental distribution of latent infection in the perivenous lymphatics. If such a thrombophlebitis continues to pile up a static, red thrombus on top of it, may throw emboli, although the infectious head of the thrombus is well fixed to the wall of the vein.

The surgeon's interest in such distinctions lies in the fact that the inflammatory thrombophlebitis is more apt to produce a fixed thrombus but with a lot of pain, edema and vasospasm, whereas the bland, aseptic thrombus is much more silent, more insidious and more apt to break loose. However, both may merge into each other and in both the control of the clotting mechanism is of great importance.

LOCALIZATION OF THROMBI

There are many small, subclinical thrombi in most of us and they seem to form at segments of stagnation due to some mechanical impediment of blood flow. Neumann²² has studied this problem extensively on cadavers. It should be noted that wherever venous return is constricted by a ligament, a tendon, a kink or a valvular stricture²³ the blood will more readily clot, although it needs some other factor such as intimal injury or increased clotting tendency to bring about the thrombus. It is likely that propagating thrombi, which become clinical when they attain a certain length, use these small phleboliths as a starting point.

The superficial saphenous system exhibits thrombi especially in varicose veins, which may remain stationary or ascend toward the sapheno-femoral junction. From the standpoint of ascending thrombosis or embolism, the thrombi of the short saphenous system are far more dangerous, because of the wide connection with the deep system, and because the varicosities of the short saphenous often represent a collateral pathway resulting from deep venous obstruction. Thrombi of superficial varicosities which represent a collateral, compensatory circulation, are very frequent. They occur in the suprapubic, or lumbar regions, in the thigh or lower leg, but the pattern of these varicosities is so characteristic that they readily point to an original deep venous obstruction. Thrombi in the plantar, supramalleolar, posterior and anterior tibial, femoral, iliofemoral, and pelvic segments give a fairly

typical clinical picture and need only be mentioned here, since a topical diagnosis is necessary to effect a surgical removal, or their elimination by division of the vein proximal to the clot.

PARAVERTEBRAL SYMPATHETIC BLOCK

That an occlusion of any vascular segment, arterial or venous, may result in vasospasm of the collateral bed is well established. But is it really necessary to inject every case of thrombosis of the extremities paravertebrally? In iliofemoral thrombosis, the typical milk-leg, the inflammatory exudate fills the vascular sheath, directly irritates the artery to constrict, and may even completely obliterate it by spasm. One can see this during surgical explorations of such segments. At this time, and even months later when a heavy, cement-like grayish cover forms around the vein, the perivascular nerves are stimulated and diffuse painful vasoconstriction results. A paravertebral block rapidly eliminates the vasospasm and helps to decrease the edema. However, we reported several years ago that small doses of Roentgen-ray, given over the inguinal or paravertebral lymphatics, will equally be effective. Certainly the sympathetic block for the bland phlebothrombosis of the lower leg does not seem indicated, in fact it may even add to the spread of the thrombus since it relaxes not only the arterial but the venous bed.²⁴

While our group has made extensive use of paravertebral blocks in arterial occlusions²⁵ its use in venous obstructions has always been limited. At present it is employed in the painful, edematous iliofemoral thrombosis with cold, cyanotic toes, suggesting arterial occlusion. In such cases the help obtained is spectacular. Considerable help has been obtained in chronic thrombophlebitic edemas which are painful, neuritic, vasospastic, and which are doubtless due to a continuous irritation of the vasomotor supply by the periphlebitic scarring. In acute axillary thrombosis following effort, the decrease in edema and pain is very gratifying.

SYMPATHETIC GANGLIONECTOMY

If paravertebral sympathetic block seems so useful, why would not a permanent interruption of the sympathetics be advisable for the chronic thrombophlebitic edemas? Such attempts have been repeatedly reported²⁶ but their widespread use has not followed. Attention should be called in the first place to the fact that the paravertebral lymph

glands are often enlarged, harbor infection, and that the removal of the chain therefore is not easy and may stir up infection. But more important is the finding that the indurations and ulcerations, while temporarily greatly improved during the first week of intense hyperemia which follows sympathectomy, do not seem to be greatly influenced by permanent sympathetic denervation. While sympathectomies are used extensively in our clinic for other conditions, chronic thrombophlebitic edema has not been included in our indications.

VENOUS STRIPPING

In 1937 I presented the case of two patients²⁷ who derived great benefit from stripping the perivenous fibrosis from the axillary and iliac veins respectively. These operations were done with the idea that most of the distress was due to a reflex vasospasm originating from the thrombosed vessel. As Leriche stated, these vessels have lost their function to conduct blood and simply act as irritable nerve plexuses maintaining reflex phenomena. It has become obvious, however, that a division of the vein with a small intervening segment is equally effective in interrupting these impulses. Perivenous stripping is equivalent to periarterial sympathectomy with its limited usefulness. It has one great advantage, however, over division in a chronic case, namely that it will not increase edema and not add to the existing difficulties of venous return.²⁸ The procedure of venous stripping or limited venous resection has been especially useful in handling the chronic cases of axillary thrombosis, whereas in the acute ones, a block of the dorsal sympathetics has been most effective.

DIVISION OF THE VEIN PROXIMAL TO THROMBOSIS

Division of the vein instead of simple or double ligation is always preferable since it seems to interrupt the perivenous nervous structures. However, it may not always be possible to do so because of anatomic difficulties. The first proximal divisions in the presence of thrombosis in our material were done on the saphenous system. The ligation of the saphenous vein in the presence of an acute saphenous thrombosis was advocated in 1930,²⁹ not only to arrest the propagation of the thrombus, but to relieve the inflamed varicosities from painful back pressure and thus permit the early mobilization of the patient with sufficient elastic support. At present, the patient who presents himself

with an acute ascending thrombosis of the saphenous vein is subjected to a typical high saphenous division. Often one finds a large saphenous bulb filled with a thrombus and occasionally one may find a loose tail of a thrombus in the iliofemoral segment. For this reason, it is advisable to aspirate the femoral vein through an eye dropper or a rectangular drinking tube³⁰ in case the long saphenous vein is found to be occluded at the sapheno-femoral junction. Naturally no retrograde injection should be made at this time, because even the simple division of the vein with its accompanying lymphatics may set up a marked periphlebitic reaction.

Not infrequently the acutely thrombosed saphenous varicosities are collaterals to a chronic deep venous obstruction. Even so they may be ligated, but the edema of the leg will persist and the patient will have to wear an elastic support. This does not detract from the protective value of the saphenous division against pulmonary embolism, but it must be clearly stated to the patient that a deep venous insufficiency will persist.

With the early recognition of plantar-vein³¹ and deep lower leg thrombosis, the latter described in so classic a form by Homans,³² the possibility arises of ligating the femoral vein below the profunda and thus not only exclude the thrombus from the circulation, but prevent an edema which would develop if the thrombus occluded both the superficial and deep branches of the femoral vein. When the typical symptoms of lower leg thrombosis occur in a patient who is hospitalized because of an operation, childbirth or a cardiac lesion, the ligature and division of superficial femoral vein below the profunda seems indicated. I am not convinced that this has to be done on both sides unless there are symptoms pointing to the involvement of both lower legs. In addition to Homans' dorsiflexion sign, which may not always be clear-cut, a slight filling of the dorsal veins, dependent cyanosis after a few minutes of dangling the feet and thus raising venous pressure, a slight warmth and tenseness of the calf compared with the other side are indicative of the side of involvement. Very exceptionally is phlebography used to establish the diagnosis of deep venous obstruction; while it may give a striking picture, when the lesion is clinically obvious, it fails you just exactly when you most need it. Furthermore, the injected diodrast or other opaque substance may produce thrombosis as reported by Homans³³ and also observed by

me in two unpublished cases. While we have used the visualization of blood-vessels off and on for many years, its use has always been greatly limited. At present, if the patient has thrown an embolus to the lungs and there is no indication from where it came, we visualize the deep venous circulation of the two lower extremities. This does not always give the answer; the embolus may have come from the pelvis or the right heart, or actually from the lower extremities, but the films may still be inconclusive.

While the division of the femoral vein below the profunda leaves very little residual damage, if the profunda and saphena are patent, the division of the common femoral vein, necessitated because of a thrombus in the profunda or in the iliac segments, has invariably resulted in permanent edema in our hands. In such cases the surgeon is confronted with a thrombus in the iliofemoral segment, which he can aspirate until he gets free flow of blood; then he tries to free the superficial and deep branches from thrombi as far as he can and finally divides the vein above the profunda with a patent proximal segment.³⁴ There are several difficulties, however, with this procedure. The proximal segment may be difficult to clear; mural thrombi may be left on the wall of the external iliac vein; the internal iliac vein may have floating thrombi in it still capable of breaking loose; the collateral circulation is not very favorable at this point.²⁰ For this reason Homans has suggested the ligation of the common iliac vein or even the vena cava. The latter procedure has been used some time ago on the Continent to prevent septic thrombi from entering the circulation in puerperal sepsis. Of 526 women who had a venous division for puerperal sepsis, 267 died, a mortality of 50.7 per cent, according to the collective review of Nürnberger.³⁵

It has seemed to me that the age of the thrombus is of paramount importance in deciding about the level of such divisions. Obviously if the thrombus has existed at the groin for a week or more, it is organizing, it is not apt to break loose, and it is difficult to remove. The fresh, soft, floating tail of an ascending thrombus is of course the dangerous one and is mostly found when it is not expected. Our practice has gradually developed into a non-interference with the clot when it has produced a massive milk-leg, since an effective ligation would mean the level of the common iliac and since emboli from this source are not too frequent.³⁶ But what is most important, an adequate

anticoagulant therapy protects the patient from embolism and still does not interfere with a recanalization of the vein.

The question immediately arises: why not use anticoagulants entirely even in the case of lower-leg thrombosis, and are they as safe and effective as the interruption of the venous current. To examine this question, we have alternately used anticoagulants alone against anticoagulants with division of the vein. Division of the vein alone as used in some clinics certainly does not protect the patient from some of the sequelae of a vein ligation. Thrombi may form both in the proximal and distal segments or the previously patent collaterals of the venous system. Fowler and I have reported such sequelae in our earlier cases.¹⁰

If one could state that anticoagulant therapy alone would safely protect the patient from embolism one could entirely dispense with surgical interruptions. The difficulty lies, however, with the close daily control of the clotting mechanism, since inadequate control is insufficient. Of 78 patients who have received the combined heparin-dicoumarol therapy, two have shown emboli; both of them with a prothrombin level of over 70 per cent of normal, obviously not an adequate protection.

A case in point is that of Alfred O., a 35-year-old radio actor, who developed cramping of the calves followed later by dyspnea, pain in the shoulder and coughing after an exploration of his right knee for an injured semilunar cartilage. His case was not diagnosed by his attendants as a lower leg vein thrombosis followed by a pulmonary infarct. He left the hospital without any swelling but entered my service two months later with a marked, tense edema of the lower leg, which promptly stopped at the level of the knee. Homans' dorsiflexion sign was positive. The femoral vein was not tender to pressure and there was not the slightest swelling of the thigh. He was primarily admitted to see whether he could not have relief from his painful edema, which necessitated the use of cane or crutch. After elevation of the foot of the bed the swelling decreased markedly and measurements were made for an elastic stocking. However, his heparin tolerance curve was absolutely flat, meaning that 10 milligrams (1 cc.) of heparin was unable to raise his coagulation time at all. This was our warning that the clot was still active. Our routine anticoagulant therapy (heparin-dicoumarol) was immediately started but heparin could not be given, since the slight symptoms which he had from the last dose were ac-

centuated to a real sensitivity reaction with the therapeutic dose, with bronchial spasm, flushing of the face and feeling of faintness. Therefore only dicoumarol was continued at the usual doses of 300, 200, and 100 milligrams for the first three days and 100 milligrams thereafter. On the seventh day, having ingested 1000 milligrams of dicoumarol, his prothrombin level had never dropped to less than 70 per cent of normal. That night he developed the classical signs and symptoms of pulmonary embolism, for which our usual emergency measures, to be described presently, were promptly administered. Next noon his right femoral vein was tied below the profunda under sodium pentothal anesthesia, since he was known to be sensitive to novocaine. The vein was free of clots at this level and was transected. The dose of dicoumarol was doubled. The swelling of the leg, which had previously decreased on elevation, did not recur. After a painful exasperating siege with hiccoughs, which seem to follow sometimes a lower lobe infarct with diaphragmatic irritation, he left the hospital with the elastic hose, the edema well controlled.

This history seems to be a strong argument for femoral vein ligation and against anticoagulant therapy. It should be pointed out that his thrombosis was at least two months old and putting him to bed may have started up a new segment of thrombosis proximal to the old one; the value of the heparin tolerance is also apparent, since an old well-organized thrombus does not give such a flat curve. He was also obviously less responsive to dicoumarol than is usual and an alert control of his clotting mechanism may have averted the embolus. It has been my feeling for a long time that the management of the clotting mechanism should be in the hands of the internist and his staff and not the surgical staff. Finally, with the clinical picture he presented, an immediate vein ligation might have been preferable.

Here is, however, a history which presents another angle of the problem:

Miss Ellen K., a 49-year-old secretary, has been under medical care for many years because of amenorrhea, renal glycosuria, and varicosities which appeared after an appendectomy. The veins on the right showed a typical valvular defect of the saphenous system but on the left there were in addition a number of valvular defects in the communicating veins of the lower leg. In spite of multiple ligations and injections, the varicosities would recur in the left calf obviously due

to the increased pressure in the deep venous system. This patient no doubt had a chronic deep venous thrombosis in the left lower leg. During the course of five years she was seen off and on by various physicians, who diagnosed recurrent attacks of pleurisy, not suspecting their embolic origin. Finally after five such attacks a ligation of the superficial femoral vein was done; the vein was thickened but patent and so was the deep branch. The swelling of the lower leg was not influenced either way. Eight months after the ligation she developed an acute phlebitis in the persistently recurring varicosities of the calf which subsided on hot compresses and sulfanilamides. There were no more emboli but the superficial veins are painful, thickened, and their circulation has been retarded.

This history shows that femoral vein ligation, especially in the presence of well-developed collaterals, so noticeably interferes with venous return that it may predispose to later attacks of thrombosis or certainly does not prevent them. This finding, which is not the only one in our series, has impressed me with the importance of early femoral vein ligations and not in the late chronic stages as Buxton and his co-workers have recently reported.²⁸

The retardation of blood flow after ligation of the femoral vein is demonstrable by determining the ankle-to-tongue circulation time with decholin. The circulation time is roughly doubled after division of the superficial and trebled after the division of the common femoral veins.

At the present writing, based on our own experience and the study of others, it is not possible to say categorically that surgical division of the vein is preferable to anticoagulant therapy. In fact, anticoagulants should always be used since when given in appropriate amounts they seem to inhibit propagation of thrombi both in the extremity or in the embolized pulmonary artery. The indication for a division of the superficial femoral vein seems clear-cut in cases of thrombosis in the lower leg. If a hospitalized patient develops cramping of the calves, pain in the sole of the foot, a Homans' sign or other symptoms of incipient deep thrombosis, the simplest and safest method is the prompt division of the superficial femoral vein. But this should be accompanied by an anticoagulant therapy, since a spreading thrombosis into the profunda or saphenous veins may result in a large, intractable edema.¹⁹ Much less clear is the indication for the ligation of the common femoral

or common iliac veins. The former leaves a crippled venous return. The latter is a larger surgical procedure and if necessary can be combined with a lumbar sympathectomy. Recently in exposing the right common iliac artery for the aspiration of a saddle-embolus of the aorta the common iliac vein was exposed with dispatch. This is not true, however, of the left side, when a ligation of the common iliac vein can be done only by men used to the technique of vascular surgery. Actually the danger of embolism from the source is slight, once the big veins of the groin are totally occluded and begin to organize.

A special problem arises in patients who have a chronic recurrent phlebitis in the same extremity extending for many years, and leading to emboli. One patient in our series, who has had a typical milk-leg following an abdominal hysterectomy, has had four grave pulmonary infarcts within a period of eight years. In the intervals, the affected extremity remained slightly tender, warmer to the touch and swollen. Courses of sulfanilamide therapy seemed ineffective; vein ligation proximal to the thrombus was suggested several times but refused. Prolonged anticoagulant therapy with dicoumarol is impractical in her case, since the patient is difficult to control. Such a patient, in whom cumbersome superficial collaterals are no problem, certainly would be benefited by a ligation of the common iliac vein.

This is not true, however, of another group of chronic cases in whom large collaterals have developed and in whom deep venous obstruction has given way to a deep venous insufficiency, because of the destruction of the valves and a partial canalization of the old thrombus.³⁷ Division of the femoral vein has been advocated for such a group recently.²⁸ It is doubtful, however, if the elimination of this deep valvular insufficiency offsets the creation of a permanent deep venous obstruction. As it is, such collateral veins frequently thrombose later and from our experience with many hundreds of such late compensatory varices, a femoral vein ligation may definitely hamper circulation. After all, it is better to have less edema and some varicosities than to obliterate all superficial collaterals as it is proposed, which in some cases, where deep collaterals are insufficient, will increase edema.

THE EXCISION OF THROMBOPHLEBITIC INDURATIONS

A real problem exists regarding the management of late thrombophlebitic edema. It is probable that if all cases of acute deep venous

obstruction were handled with dispatch and with an eye on preventing chronic edema, the late thrombophlebitic indurations and ulcerations would not be as prevalent. Early vein ligations, anticoagulant therapy, sympathetic block, elastic support from toes to groin by fitted stockings will do much to prevent these late sequelae. Attention should be called to the great benefit derived from the use of heparin in early edemas, since these edemas as Zimmermann and I³⁸ have shown both histologically and chemically, contain much protein, much fibrin, all of which is precipitated in the tissues. Such clotted plasma then is very difficult to absorb, clogs the lymphatics, sets up a connective-tissue reaction and results in the hard, brawny indurations and ulcerations so well known to you. The patches of acute lymphedema which are stirred up by cutaneous infections or foci elsewhere keep aggravating the lesion until large plaques of cement-hard tissue, with scalloped borders develop. Severe paroxysmal pain suggests the formation of neuromas in the scar. Bed rest, hot fomentations, glycerin casts, mecholyl or salt iontophoresis may be of some benefit. But the only procedure that will get rid of this chronic inflammatory fibrosis with ulceration is a thorough excision of the entire area, down to the fascia, which in our more recent experience need not be excised. The defect is then immediately covered with a split-thickness skin graft, which is secured in place both by the help of sutures and by plasma-thrombin glue which nourishes the graft and helps its early vascularization.³⁹ The only difficulty I have had with such grafts is late development of small thrombi under the graft, when the perforators have not been thoroughly ligated, or a break in the graft if edema of the leg is not controlled by elastic support. This method is still the best under the circumstances, but again it should be stressed that early adequate management should obviate most of these late, incapacitating sequelae.

THE SURGICAL TREATMENT OF PULMONARY EMBOLISM

In a study conducted a few years ago, Jesser and I⁴⁰ found that out of 100 cases of fatal pulmonary embolism eight patients will die instantly or within 10 minutes so that no help can be given them; but 60 will live from one hour to several days after the sudden onset of symptoms. We suggested a certain routine of emergency which is posted on every floor (Table II) and which has been now employed in 45 patients with severe symptoms as recognized by the nurses. Ten

TABLE II
PULMONARY EMBOLISM

Recognition

Sudden onset of shock with rapid, weak pulse, restlessness, difficult, rapid breathing, sweating and pallor, pain in chest, fainting, collapse or unconsciousness. Apt to be in a patient who has phlebitis or is convalescing from an operation or delivery or is a known cardiac.

Emergency Treatment

By Nurse

1. Place in semi-sitting position.
2. Start oxygen by catheter or mask immediately. Tanks are on each floor.
3. Give 1/75 grain atropine sulfate, hypodermically, immediately.
4. Call intern.

By Intern

1. Give a second dose of 1/60 to 1/75 grain atropine sulfate intravenously (if previous injection of atropine has not caused flushing of face and dilation of pupil).
2. In any case give 1/2 grain papaverine hydrochloride intravenously.
3. Repeat atropine and papaverine three or four times a day.
4. Order portable chest film and electrocardiogram.

Note:

Morphine, adrenalin or digitalis may aggravate the condition.

Above treatment is useful even if patient is suffering from some other condition such as coronary occlusion or a cerebral vascular accident.

TABLE III
THE SURGICAL TREATMENT OF VENOUS THROMBOSES

| Method of treatment | Number of cases | Results | |
|--|-----------------|---------|------|
| | | Good | Fair |
| Paravertebral block ¹ | 78 | 51 | 27 |
| Sympathetic ganglionectomy | 2 | | 2 |
| Division of femoral vein ² | 25 | 15 | 10 |
| Excision and graft ³ of thrombophlebitic induration . . . | 25 | 23 | 2 |
| | 130 | 89 | 41 |

¹ Done less frequently now. The large number of indifferent (fair) results are due to improper selection of cases.

² The ligation of common femoral vein invariably resulted in permanent edema.

³ In 2 cases the graft broke down months or years later.

of these died and six had autopsies. All six had large totally obstructing clots in the pulmonary artery or in the right ventricle. It seems convenient to divide the treatment of pulmonary embolism into three stages. In the first stage, the reflex phenomena which operate on the heart, the bronchi, the pulmonary arterial tree and the gastrointestinal tract are interrupted by the comparatively large doses of papaverine and atropin. Oxygen is administered by a Boothby mask or a modification of the rubber mask made out of cellulose acetate, for the cyanosis or dyspnea. Some dramatic recoveries have been observed from this procedure.

If the patient survives the initial attack the second phase of treatment starts by the administration of anticoagulants. It has been shown by the postmortem studies of Belt¹¹ and also is clinically recognizable that the primary occluding embolus may grow proximally or distally, involving larger and larger segments of the lung so that dyspnea and the x-ray findings suggest more and more involvement of the arterial tree. These are not new emboli, but superimposed thrombi on the initially smaller embolus. Heparin-dicoumarol therapy is definitely indicated in all patients who have suffered a pulmonary embolus. It may occasionally increase the hemoptysis. It should also protect the patient from a propagating thrombus at the site of the primary blood-clot. Since approximately 40 per cent of pulmonary emboli occur without any indication of a peripheral venous thrombosis³⁰ a thorough search should now be made for the origin of the embolus. Unless it is in the pelvis or in the right heart, it is apt to be in the lower leg and as previously stated this can be readily excluded from the circulation by a division of the femoral vein.

In spite of the combined therapy with papaverine, atropin, oxygen, heparin and dicoumarol, some patients who made an initial recovery, slowly fail and die on the second to fourth day after the initial attack. Unquestionably they die of right heart failure, since the combined antispasmodic and anticoagulant therapy has been unable to decrease the large resistance in the pulmonary arterial bed. While the attempts to extract a pulmonary embolus in the early stages have either come too late or may have been unnecessary, such slowly fatal pulmonary emboli, as Pilcher⁴² pointed out, can only be saved by pulmonary embolectomy.

The mortality statistics of such an operation are very sad. When

last studied by us, 9 out of 134 cases survived. It must be remembered, however, that these were moribund cases operated on in an emergency.

With the renewed interest in exposing the root of the large vessels which has come about with the ligation of the patent ductus arteriosus and with operating on patients who are by no means moribund, but who show a gradually increasing cor pulmonale, with its physical and electrocardiographic findings, a very limited indication for pulmonary embolectomy still exists. Pilcher has described the difficulties encountered in operating too early when the patient is on the road to recovery or too late, when the patient might have been saved by not waiting so long. Technically the operation is not too difficult. On large surgical services, the senior surgical resident should be trained on the cadaver to perform such a procedure and a team may have to be ready for 24 hours of the day waiting for an optimal time to operate.

I discussed this indication not because of any personal experience, but because of the general surgical opinion that pulmonary embolectomy is useless and should be completely discarded. Watching some of our patients die slowly in spite of conservative therapy encourages me to try such an operation in the very occasional suitable case.

CONCLUSIONS

It seems appropriate here to sum up the experience of our group with surgical measures directed against thrombo-embolism. As stated before, these are employed in conjunction with other measures, chiefly the use of anticoagulants. The indications for paravertebral block at present are the existence of a demonstrable arterial or venocapillary spasm with cyanosis, diminished pulsation, intense stocking or glove-like pain. This clot is mostly in the iliofemoral segment with perivenous inflammatory reaction, the typical iliofemoral thrombophlebitis. There seems to be no special advantage in using this block on patients suffering from the bland, quiet type of thromboses of the lower leg.

Sympathetic ganglionectomy has been done in only two patients with a chronic phlebitic induration and ulceration. While both ulcers healed, neither the edema nor the character of the thin scar bridging the defect had been influenced. The scars broke down later and had to be widely excised.

Division of the femoral vein below the profunda has been found to be an excellent measure: (1) in patients who have had a pulmonary

embolus the source of which was localized to a thrombus below the knee; (2) in patients who suddenly experienced the classical symptoms of plantar-vein or lower-leg thrombosis without any clinical involvement of the femoral segment. Such patients, as emphasized by Bauer¹³ may well have a floating, non-obstructive thrombus in the femoral vein but this causes no clinical symptoms and is dangerous as far as its tendency to break loose. Division of the common femoral or common iliac vein in the presence of a typical acute milk-leg has not been done in this group except in a few cases and I am quite uncertain about its value. In the old chronic cases, with established collateral circulation and a deep venous valvular insufficiency I have not been able to see any indication for it. Ligation of the vena cava in the occasional bilateral iliac thrombosis with emboli may save life and seems to result in no additional circulatory impairment. The approach is that to a muscle-splitting extraperitoneal lumbar sympathectomy.

Excision of a chronic thrombophlebitic ulcer with induration, followed by a dermatome graft, is a very valuable procedure and saves the patient much loss of time and suffering. Naturally, the chronic edema will not be influenced and elastic support must be worn, probably continuously. (Table III)

The slowly fatal pulmonary embolus might be aspirated from the pulmonary artery surgically.

SUMMARY

The factors responsible for the intravascular clotting of blood must be always considered and controlled even if surgical measures are indicated. These measures therefore constitute only one phase of treatment. The surgeon must try to accelerate retarded venous return, not operate in the presence of sensitization phenomena, and attempt to control the clotting mechanism by anticoagulants. The distinction between infectious thrombophlebitis and aseptic, bland phlebothrombosis is not always possible. Both may exist simultaneously in the same patient. The segmental localization of thrombi is often determined by mechanical impediments of blood flow, produced by ligaments, tendons or angulations. Thrombi are well recognizable in the saphenous, plantar, deep lower leg, iliofemoral and pelvic veins, and their treatment does depend on their location. Paravertebral sympathetic block is used in acute and chronic iliofemoral thromboses exhibiting vasospasm. Sympathetic gang-

lionectionomy for venous thromboses of the extremities and their sequelae has not been especially helpful. Division of the superficial femoral vein in cases of thrombosis of the lower leg is an excellent procedure. It not only prevents more emboli from this source but inhibits the development of an ascending thrombosis with permanent edema. Divisions at a higher level have not yet been routinely adopted, since anticoagulant therapy seems at least as efficacious and probably not as productive of late edema. Excision of thrombophlebitic indurations and ulcerations, followed by a split-thickness skin graft is very useful. The surgical treatment of pulmonary embolism is most rarely indicated, but in the slowly fatal cases may save a life.

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